



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: 3,4-DISUBSTITUTED-PHENYLSULPHONAMIDES AND THEIR THERAPEUTIC USE				
(57) Abstract				
3,4-Disubstituted benzenesulphonamides of general formula (i), in which R <sub>3</sub> represents arylalkyl, heteroarylalkyl, heterocycloalkyl, COR <sub>7</sub> , S(O) <sub>m</sub> R <sub>7</sub> , optionally substituted C <sub>1-6</sub> alkyl, R <sub>4</sub> represents arylalkyl, heteroarylalkyl or heterocycloalkyl, and the other substituents are as defined in Claim 1, have therapeutic utility via phosphodiesterase IV inhibition.				
<p style="text-align: right;">(i)</p>				

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3,4-DISUBSTITUTED-PHENYLSULPHONAMIDES  
AND THEIR THERAPEUTIC USE

Field of the invention

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The present invention relates to novel sulphonamide compounds and pharmaceutically acceptable salts thereof, processes for their production and formulation and use as pharmaceuticals.

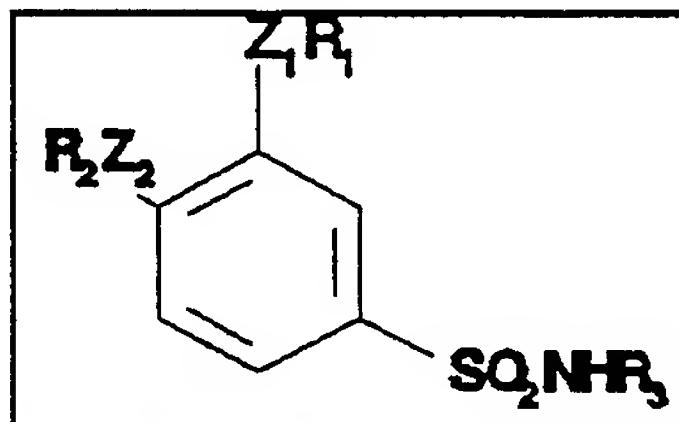
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Description of the prior art.

15

International Patient Application WO 94/02465 discloses inhibitors of phosphodiesterase IV and TNF including sulphonamides of formula:-

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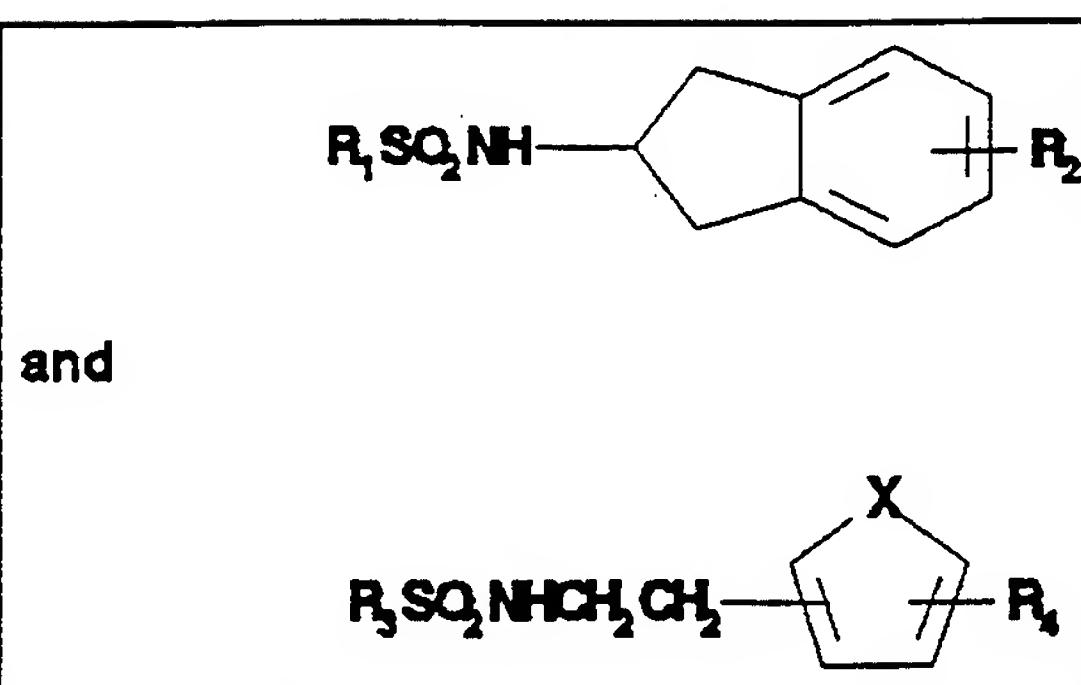
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wherein R<sup>1</sup> is alkyl, alkenyl, cycloalkyl, cycloalkenyl, cyclothioalkyl, or cyclothioalkenyl ; R<sup>2</sup> is lower alkyl ; R<sup>3</sup> is aryl or heteroaryl; Z<sup>1</sup> and Z<sup>2</sup> are independently oxygen or sulphur. The only sulphonamide exemplified is N-(2-chlorophenyl)-3-cyclopentyloxy-4-methoxybenzenesulphonamide.

European Patent Application 0 306 846 discloses sulphonamides of formula:-

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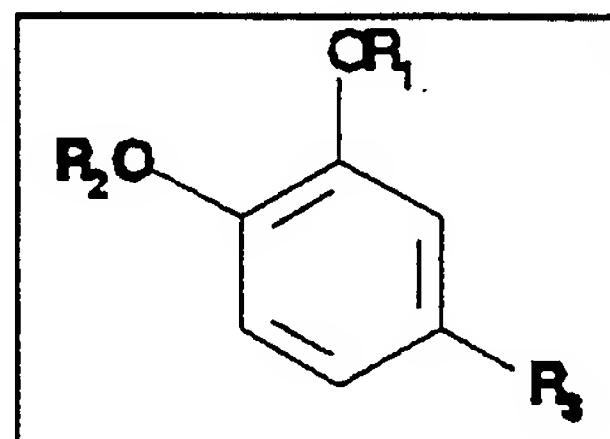
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10 as thromboxane A<sub>2</sub> antagonists. European Patent Application 0589 037 discloses structures similar to the above also as thromboxane A<sub>2</sub> antagonists.

15 United States Patents 5,283,352 and 4,963,590 disclose compounds of formula

20



25 in which R<sub>3</sub> may be sulphonamide, as catechol-O-methyl transferase inhibitors.

Phosphodiesterases regulate cyclic AMP concentrations. Phosphodiesterase IV has been demonstrated to be a principal regulator of cyclic AMP in respiratory smooth muscle and inflammatory cells. [See Torphy and Creslinski, Molecular Pharmacology 37, 206, (1990); Dent et al British Journal of Pharmacology, 90 163p (1990)]. Inhibitors of phosphodiesterase IV have been implicated as being bronchodilators and asthma-prophylactic agents and as agents for inhibiting eosinophil accumulation and the function of eosinophils [See for example Giembycz and Dent, Clinical and Experimental Allergy 22 337 (1992)] and

for treating other diseases and conditions characterised by, or having an etiology including, morbid eosinophil accumulation. Inhibitors of phosphodiesterase IV are also implicated in treating inflammatory diseases, proliferative 5 skin disease and conditions associated with cerebral metabolic inhibition.

Excessive or unregulated production of Tumour Necrosis Factor (TNF), a serum glycoprotein, has been implicated in 10 mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory 15 distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to 20 infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC, (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as 25 multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or 30 strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte 35 activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by

such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

5

Cytokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation.

10 Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in

15 a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as Kupffer and glial cells, have also been implicated in maintenance of the HIV infection.

20 These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al, *The Immunopathogenesis of HIV Infection, Advances in Immunology*, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in

25 monocytes and/or macrophages [See Poli et al, *Proc. Natl. Acad. Sci.*, 87:782-784, (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

30 TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

35 TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production in vitro in human monocytes and natural killer

cells. [See Riipi et al., *Infection and Immunity*, 58(9):2750-54, (1990); and Jafari et al., *Journal of Infectious Diseases*, 164:389-95, (1991). See also Wasan et al., *Antimicrobial Agents and Chemotherapy*, 35, (10):2046-5 48, (1991); and Luke et al., *Journal of Infectious Diseases*, 162:211-214, (1990)].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in 10 mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

15 US-A-4948809 discloses thromboxane antagonists including inter alia, arylsulphonamides. They are proposed for the treatment of cardiovascular diseases and asthma. There is no specific disclosure therein of one possible combination of substituents, comprising phenylsulphonamides 20 in which the phenyl group is di(alkoxy)-substituted, and the N substituents are (i) phenyl(C<sub>1-4</sub> alkyl) and the phenyl group is 4-substituted by alkyl/alkenyl, formylalkyl, hydroxyalkyl, or -D-R<sub>3</sub> where D is -CO- or -CHOH- and R<sub>3</sub> is H, alkyl, hydroxyalkyl or alkylcarboxylic acid, and (ii) H, 25 alkyl, acyl, aralkyl or aralkenyl, any aryl moiety being optionally substituted by halogen, alkyl, alkoxy, OH, CF<sub>3</sub>, CN, NO<sub>2</sub>, NH<sub>2</sub>, alkylamino, dialkylamino, acylamino, acyl or azido.

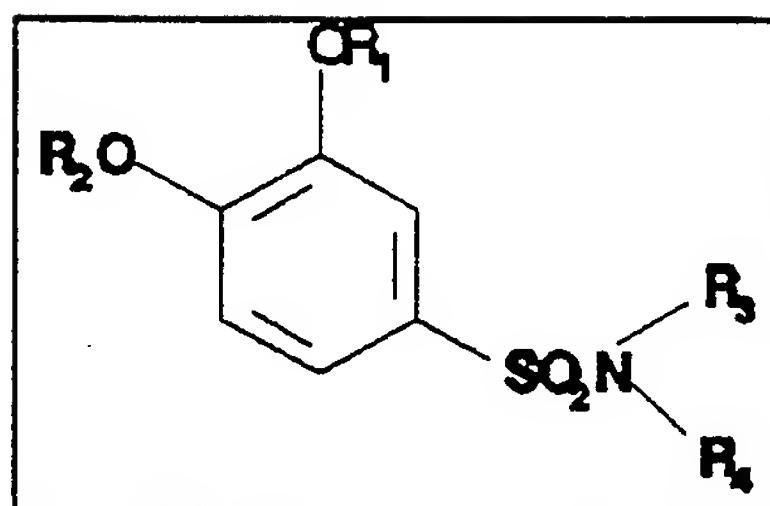
30 Summary of the invention

It has been found that novel compounds of formula (i) have utility to treat disease states, for example disease states associated with proteins that mediate cellular activity, 35 for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):

5

(i)

10



in which R<sub>1</sub> represents C<sub>1-6</sub> alkyl (optionally substituted with one or more substituents chosen from amongst halogen, 15 C<sub>1-6</sub> alkoxy, aryloxy, arylalkyloxy, C<sub>1-6</sub> alkylamino, arylalkylamino or arylamino) or cycloalkyl (optionally substituted with one or more substituents chosen from amongst halogen, C<sub>1-6</sub> alkoxy, aryloxy, arylalkyloxy, C<sub>1-6</sub> alkylamino, arylalkylamino or arylamino);

20

R<sub>2</sub> represents C<sub>1-3</sub> alkyl optionally substituted with halogen;

25 R<sub>3</sub> represents arylalkyl, heteroarylalkyl, heterocycloalkyl, COR<sub>7</sub>, S(O)<sub>m</sub>R<sub>7</sub>, C<sub>1-6</sub> alkyl optionally substituted with one or more substituents chosen from amongst hydroxy, C<sub>1-6</sub> alkoxy, -CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CN, carbonyl oxygen, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>n</sub>R<sub>7</sub>;

30 R<sub>4</sub> represents arylalkyl, heteroarylalkyl or heterocycloalkyl;

when R<sub>3</sub> and/or R<sub>4</sub> represents arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion may be optionally substituted with one or more substituents chosen from amongst CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub>, hydroxy, C<sub>1-6</sub> alkoxy, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>n</sub>R<sub>7</sub>, -CN or carbonyl oxygen and/or

the aryl/heteroaryl/heterocyclo portion may be optionally substituted with one or more substituents C0-6 alkyl-R<sub>11</sub>;

R<sub>5</sub> and R<sub>6</sub>, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C<sub>1-6</sub> alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl heteroarylcarbonyl, heterocyclocarbonyl or C<sub>1-6</sub> alkylsulphonyl, provided that when R<sub>5</sub> is C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or C<sub>1-6</sub> alkylsulphonyl, R<sub>6</sub> is not C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy carbonyl, 15 arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or C<sub>1-6</sub> alkylsulphonyl;

R<sub>7</sub> represents aryl, heteroaryl, heterocyclo or C<sub>1-6</sub> alkyl, 20 any of which may be optionally substituted with one or more substituents chosen from amongst halogen, aryl, heteroaryl, heterocyclo, C<sub>1-6</sub> alkoxy, hydroxy, CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub>, NR<sub>5</sub>R<sub>6</sub> or carbonyl oxygen;

R<sub>8</sub> represents C<sub>1-6</sub> alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R<sub>9</sub> and R<sub>10</sub>, which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo, C<sub>1-6</sub> alkyl, 30 arylalkyl, heteroarylalkyl, heterocycloalkyl;

R<sub>11</sub> represents H, aryl, heteroaryl, heterocyclo, hydroxy, C<sub>1-6</sub> alkoxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, -CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, CONR<sub>9</sub>R<sub>10</sub>, 35 halogen, -CN, -NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>n</sub>R<sub>7</sub>, -CN or carbonyl oxygen;

m represents 1-2;

n represents 0-2;

and pharmaceutically acceptable salts thereof.

5 Description of the Invention

Preferred compounds of the invention include those in which, independently or in any combination:

10 R<sub>1</sub> is C<sub>1-6</sub> alkyl (optionally substituted with aryloxy) or cycloalkyl;

R<sub>2</sub> is methyl optionally substituted with halogen;

15 R<sub>3</sub> is arylalkyl, heteroarylalkyl, COR<sub>7</sub>, SO<sub>2</sub>R<sub>7</sub> or C<sub>1-6</sub> alkyl (optionally substituted with one or more substituents chosen from amongst hydroxy, CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, CN, carbonyl oxygen, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub> or SO<sub>2</sub>R<sub>7</sub>);

20 R<sub>4</sub> is arylalkyl or heteroarylalkyl;

when R<sub>3</sub> and/or R<sub>4</sub> represents arylalkyl or heteroarylalkyl, the aryl or heteroaryl portion may be optionally substituted with one or more substituents C<sub>0-6</sub> alkyl-R<sub>11</sub>;

25

R<sub>5</sub> and R<sub>6</sub>, which may be the same or different, are H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylsulphonyl, aryl, heteroaryl, arylsulphonyl, heteroarylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylalkyl or heteroarylalkyl;

30

R<sub>7</sub> is C<sub>1-6</sub> alkyl (optionally substituted with CN, CO<sub>2</sub>H, CO<sub>2</sub>R<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, carbonyl oxygen or NR<sub>5</sub>R<sub>6</sub>), aryl or heteroaryl;

35

R<sub>8</sub> is C<sub>1-6</sub> alkyl;

$R_9$  and  $R_{10}$ , which may be the same or different, are H,  $C_{1-6}$  alkyl, arylalkyl or heteroarylalkyl;

5  $R_{11}$  is aryl, heteroaryl, hydroxy,  $C_{1-6}$  alkoxy, CN,  $CO_2H$   $CO_2R_8$ ,  $CONR_9R_{10}$ ,  $SO_2NR_9R_{10}$ , carbonyl oxygen,  $NR_5R_6$ ,  $COR_7$  or  $SO_2R_7$ .

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Certain of the compounds of 10 formula (i) which contain an acidic group form base salts. Suitable pharmaceutically acceptable base salts include metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

15 Certain of the compounds of formula (i) which contain an amino group form acid addition salts. Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically 20 acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphate,  $\alpha$ -ketoglutarate,  $\alpha$ -glycerophosphate and glucose-1-phosphate. The pharmaceutically acceptable salts 25 of the compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that some of the compounds of formula (i) may exist in more than one tautomeric form. This invention extends to all 30 tautomeric forms.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in a compound of formula (i) can 35 give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers,

including enantiomers, and diastereoisomers and mixtures including racemic mixtures thereof.

When used herein the term alkyl whether used alone or when used as a part of another group includes straight and branched chain alkyl groups containing up to 6 atoms. Alkyl-R<sub>11</sub> means that the R<sub>11</sub> substituent may be attached at any position on the alkyl group. Alkoxy means an alkyl-O-group in which the alkyl group is as previously described. Aryloxy means an aryl-O-group in which the aryl group is as defined below. Arylalkyloxy means an aryl-alkyl-O-group. Alkylamino means an alkyl-N-group in which the alkyl group is as previously defined, arylamino means aryl-N- and heteroaryl amino means an heteroaryl-N-group (aryl and heteroaryl defined below). Cycloalkyl includes a non-aromatic cyclic or multicyclic ring system of about 3 to 10 carbon atoms. The cyclic alkyl may optionally be partially unsaturated. Aryl indicates carbocyclic radicals containing about 6 to 10 carbon atoms. Arylalkyl means an aryl-alkyl-group wherein the aryl and alkyl are as described herein. Heteroarylalkyl means a heteroaryl-alkyl group. Heterocycloalkyl means a heterocyclo-alkyl group. Alkyl amide includes both monoalkyl and dialkyl amides, in which the alkyl groups (previously described) may be the same or different. Alkylcarbonyl means an alkyl-CO-group in which the alkyl group is as previously described. Arylcarbonyl means an aryl-CO-group in which the aryl group is as previously described. Arylsulphonyl means an aryl-SO<sub>2</sub>-group in which the aryl group is as previously described. Heteroarylsulphonyl means a heteroaryl-SO<sub>2</sub>-group and heterocyclosulphonyl means a heterocyclo-SO<sub>2</sub>-group. Heteroarylcarbonyl means a heteroaryl-CO-group and heterocyclocarbonyl means a heterocyclo-CO-group. Alkoxy carbonyl means an alkoxy-CO-group in which the alkoxy group is as previously described. Alkylsulphonyl means an alkyl-SO<sub>2</sub>-group in which the alkyl group is as previously described. Carbonyl oxygen means a -CO-group.

It will be appreciated that carbonyl oxygen can not be a substituent on an aryl or heteroaryl ring. Carbocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system which may be saturated or partially 5 unsaturated. Heterocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system (which may be saturated or partially unsaturated) wherein one or more of the atoms in the ring system is an element other than carbon chosen from amongst nitrogen, oxygen or sulphur 10 atoms. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Heterocyclo means about a 5 to about a 15 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Halogen means fluorine, chlorine, bromine or iodine.

20 "TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or 25 IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF- $\beta$  (also known as lymphotoxin) has close structural homology 30 with TNF- $\alpha$  (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- $\alpha$  and TNF- $\beta$  are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically 35 delineated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which 5 comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety 10 of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, 15 Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the 20 myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile 25 dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. 30 Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

35 The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased

replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, Herpes zoster and Herpes simplex.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is fungal meningitis.

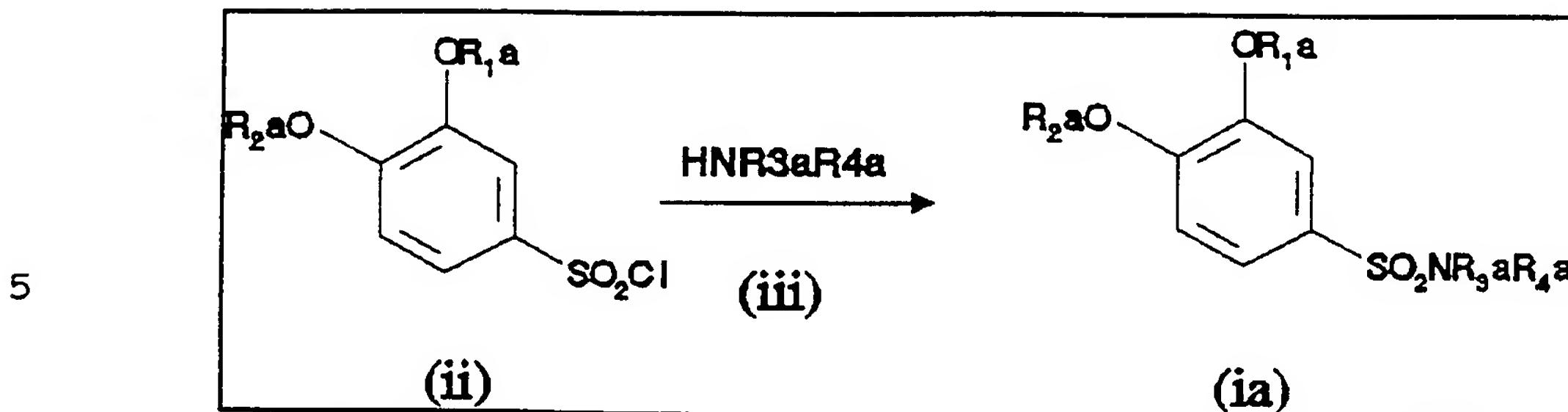
The compounds of formula (i) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally

be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

5 The invention further provides a process for the preparation of a compound of formula (i), in which R<sub>1</sub>-R<sub>11</sub> and m-n are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various compounds described below,  
10 and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in  
15 the art. For specific details, see Protective Groups in Organic Synthesis, Wiley Interscience, TW Greene.  
Thus the process for preparing compounds of formula (i) in which R<sub>3</sub> contains a -CO<sub>2</sub>H comprises deprotecting (for example by hydrolysis) a compound of formula (i) in which  
20 R<sub>3</sub> contains an appropriate -CO<sub>2</sub>R wherein R represents a suitable protecting group (eg methyl).

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by  
25 conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may be performed using the appropriate homochiral starting material.

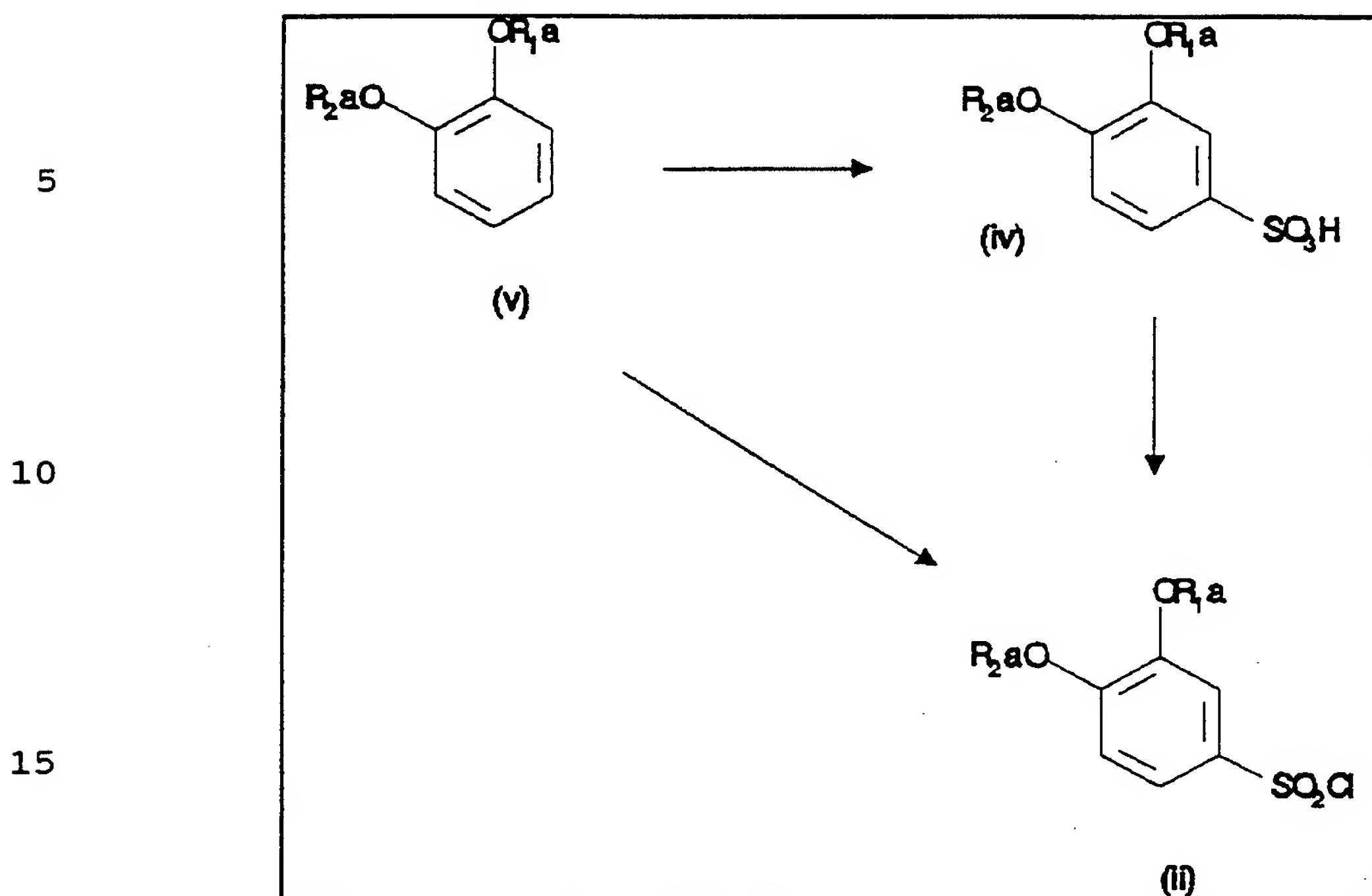
30 A process for the preparation of a compound of formula (ia) comprises reaction of an appropriate sulphonyl chloride of formula (ii) with a suitable amine of formula (iii)



wherein  $R_{1a}$  represents  $R_1$  as defined in relation to formula  
 10 (i) or a group convertable to  $R_1$  and  $R_{2a}-R_{4a}$  similarly  
 represent  $R_2-R_4$  or groups convertable to  $R_2-R_4$  respectively;  
 and thereafter, if required, converting any group  $R_{1a}$  to  $R_1$ ,  
 and/or  $R_{2a}$  to  $R_2$  and/or  $R_{3a}$  to  $R_3$  and/or  $R_{4a}$  to  $R_4$ .

15 The reaction of a sulphonyl chloride of formula (ii) with  
 an amine of formula (iii) may be carried out under any  
 suitable conditions known to those skilled in the art.  
 Favourably the reaction is carried out in the presence of  
 a suitable base, for example an amine such as  
 20 triethylamine, preferably in an appropriate solvent such as  
 dichloromethane.

Sulphonyl chlorides of formula (ii) are either commercially  
 available or are prepared using standard procedures known  
 to those skilled in the art. For example a sulphonyl  
 25 chloride of formula (ii) may conveniently be prepared from  
 the appropriate sulphonic acid (iv) by treatment with a  
 suitable agent such as thionyl chloride or oxalyl chloride.  
 An appropriate sulphonic acid may be prepared from a  
 compound of formula (v) by sulphonylation using an  
 30 appropriate sulphonylating agent, for example  
 chlorosulphonic acid. Alternatively, a sulphonyl chloride  
 of formula (ii) may be prepared directly from a compound of  
 formula (v) by using excess chlorosulphonic acid. Compounds  
 of formula (v) are either commercially available or may be  
 35 prepared by standard procedures known to those skilled in  
 the art.

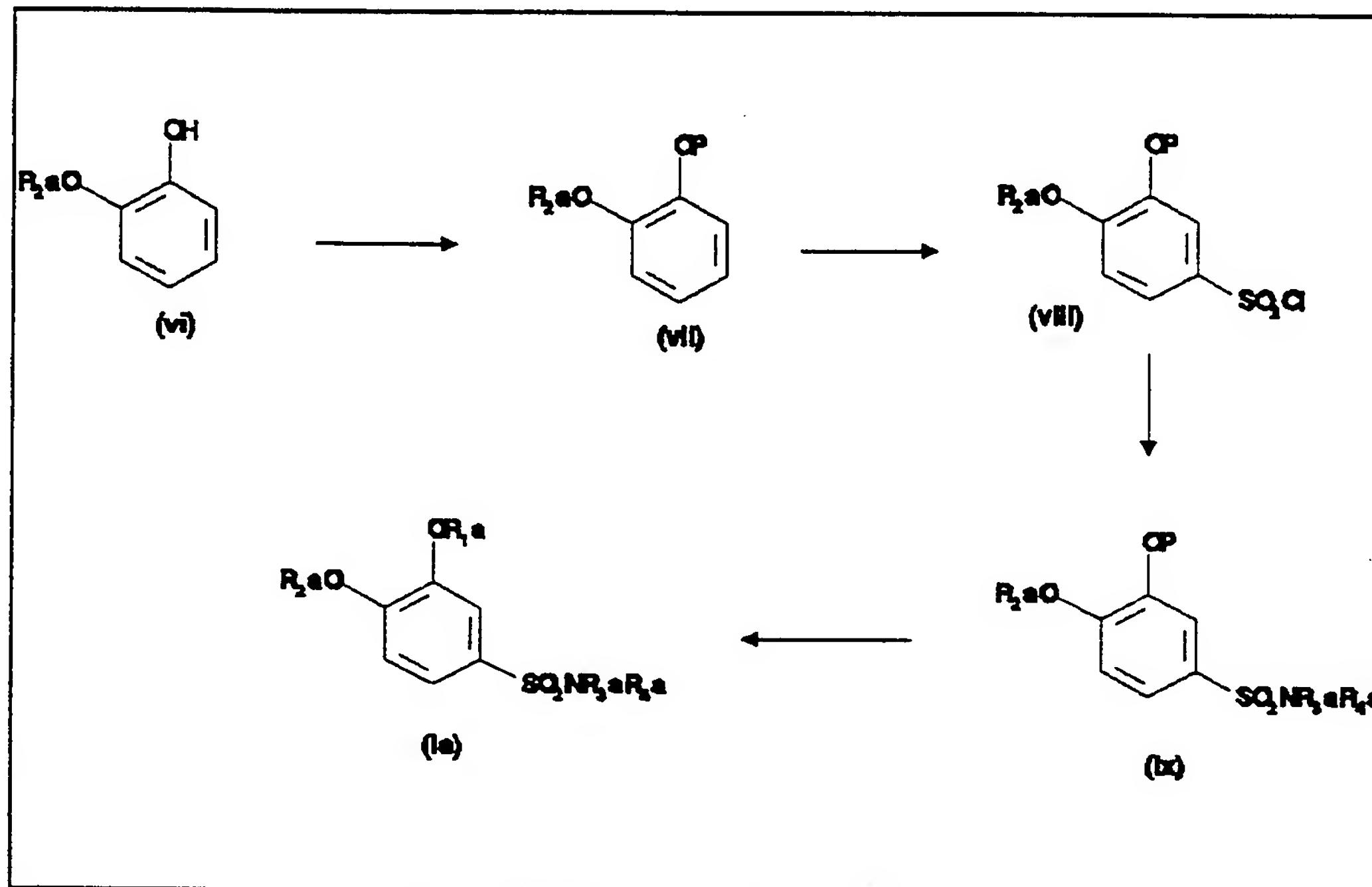


Amines of formula (iii) are either commercially available,  
 20 previously described compounds or are prepared using standard procedures known to those skilled in the art. Some of the amines of formula (iii) are conveniently prepared by reductive amination of an appropriate carbonyl compound with a suitable amine. This amination may be carried out  
 25 under any suitable standard conditions known to those skilled in the art.

An alternative method for the preparation of compounds of formula (ia) is shown below. This method involves the protection of an appropriate phenol of formula (vi) with a suitable protecting group (for example methanesulphonyl) under standard conditions known to those skilled in the art to provide a compound of formula (vii) and subsequent conversion to a sulphonyl chloride of formula (viii) by 35 sulphonylation or chlorosulphonylation as described earlier. Reaction of sulphonyl chloride (viii) with an amine of formula (iii) as described earlier provides a compound of

formula (ix). Deprotection under standard conditions known to those skilled in the art, followed by alkylation under standard conditions known to those skilled in the art provides a compound of formula (ia).

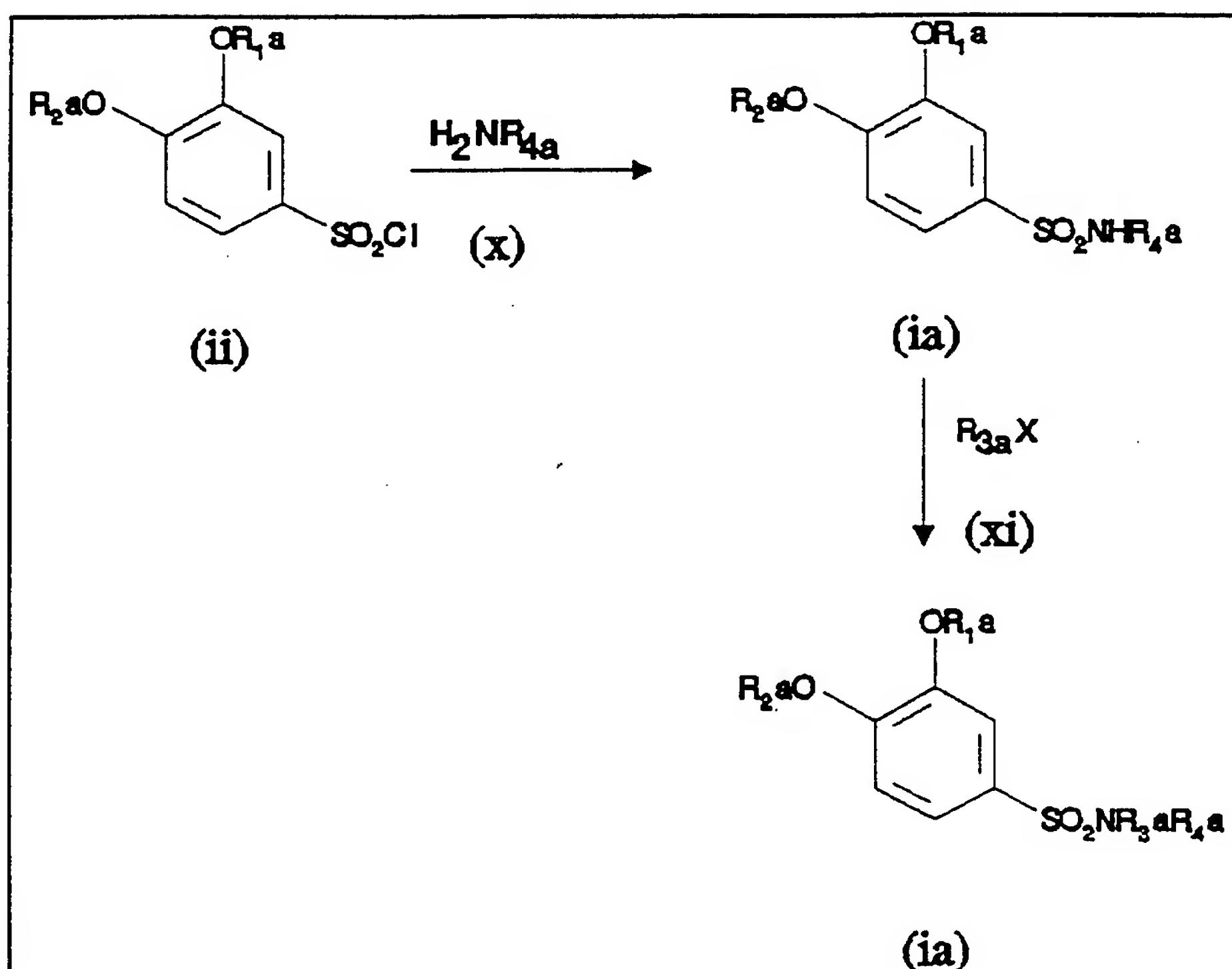
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A compound of formula (ia) may also be prepared by reaction of a sulphonyl chloride of formula (ii) with an amine of formula (x) to provide a compound of formula (ia) in which R<sub>3</sub> is H, followed by reaction with an appropriate agent of formula (xi).

15

20



wherein  $R_{1a}$ - $R_{4a}$  are as defined earlier and X represents a suitable leaving group such as a halogen. The reaction of a sulphonyl chloride of formula (ii) with an amine of formula (x) may be carried out under any suitable conditions known to those skilled in the art. Favourably the reaction is carried out in the presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane.

Amines of formula (x) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. The reaction of a compound of formula (i) in which  $R_3$  is H with an agent of formula (xi) may be carried out under any suitable conditions known to those skilled in the art. Favourably the reaction is carried out using an appropriate base, such as sodium hydride, preferably in an appropriate solvent such as dimethylformamide. An agent of formula (xi) may be an alkylating agent such as propyl bromide, an

acylating agent such as benzoyl bromide or a sulphonylating agent such as methanesulphonyl chloride. Agents of formula (xi) are either commercially available, previously described compounds or are prepared using standard 5 procedures known to those skilled in the art.

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which  $R_4$  contains an alkoxy group 10 may be prepared by appropriate alkylation of a compound in which  $R_4$  contains a hydroxy group.

A compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a 15 pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

20 Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

25

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may 30 administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

35

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal

injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

5

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions 10 or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is 15 preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional 20 excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example 25 starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional 30 methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

35 Such operations are of course conventional in the art. The tablets may be coated according to methods well known in

normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for 5 example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, 10 hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters 15 such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

20 Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the 25 particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and 30 bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

35 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either

suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

5

Advantageously, adjuvants such as local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

20

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

25

Compounds of formula (i), or if appropriate a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

30

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

5

10 Suitably, the compound of formula (i), or if appropriate a pharmaceutically acceptable salt thereof, will compromise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

15

15 The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general 20 guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total 25 daily dosage for a 70kg adult is in the range of about 0.1 to 1000mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy 30 may extend for a number of weeks or months.

When used herein the term "pharmaceutically acceptable" encompasses materials suitable for both human and veterinary use.

Intermediate 1 N-(4-Pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

4-(Aminomethyl)pyridine (0.51ml) was added to a solution of 5 3,4-dimethoxybenzenesulphonyl chloride (1.08g) and triethylamine (0.96ml) in dichloromethane (30ml) at room temperature under a nitrogen atmosphere. The solution was stirred for 16 hours and then concentrated in vacuo. The residue was purified by column chromatography on 10 silica, eluting with 10% hexane in ethyl acetate, to provide the title compound (236mg) as an off-white solid.

TLC  $R_f$  0.18 (1% acetic acid/5% methanol in ethyl acetate)

15 The following compounds were prepared from the appropriate sulphonyl chloride and amine, using the above procedure.

Intermediate 2 N-(3-Pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

20 Purification by column chromatography on silica, eluting with 20% ethyl acetate in dichloromethane provided the title compound (400mg) as an oil.

25 TLC  $R_f$  0.15 (20% ethyl acetate in dichloromethane)

Intermediate 3 N-(2-Pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

30 Purification by column chromatography on silica, eluting with 10% hexane in ethyl acetate and recrystallization from ethyl acetate yielded the title compound (246mg) as an off-white solid.

35 TLC  $R_f$  0.20 (10% hexane in ethyl acetate)

Intermediate 4 N-Benzyl-3,4-

## dimethoxybenzenesulphonamide

Recrystallization from ethyl acetate/hexane afforded the title compound (330mg) as a white solid.

5

TLC  $R_f$  0.25 (30% ethyl acetate in hexane)

Intermediate 5 N-(2,6-Dichlorobenzyl)-3,4-dimethoxybenzenesulphonamide

10

Purification by column chromatography on silica, eluting with 40% ethyl acetate in hexane afforded the title compound (1.0g) as a pale yellow solid.

15

TLC  $R_f$  0.2 (40% ethyl acetate in hexane)

Intermediate 6 N-Phenethyl-3,4-dimethoxybenzenesulphonamide

20

Purification by column chromatography on silica, eluting with 50% ethyl acetate in hexane yielded the title compound (2.19g) as an oil which crystallized on standing.

TLC  $R_f$  0.33 (50% ethyl acetate in hexane)

25

Intermediate 7 N-Furfuryl-3,4-dimethoxybenzenesulphonamide

30

Recrystallization from ethyl acetate/hexane gave the title compound (5.04g) as white crystals.

TLC  $R_f$  0.45 (60% ethyl acetate in hexane)

35

Intermediate 8 N-Benzyl-3-methanesulphonyloxy-4-methoxybenzenesulphonamide

Recrystallization from ethyl acetate/hexane afforded the title compound (14mg).

TLC  $R_f$  0.2 (50% ethyl acetate in hexane)

5

Intermediate 9 N-Furfuryl-3-methanesulphonyloxy-4-methoxybenzene sulphonamide

TLC  $R_f$  0.26 (60% ethyl acetate in hexane)

10

Intermediate 10 N-(2-(2-Pyridyl)ethyl)-3,4-dimethoxybenzenesulphonamide

15 Purification by column chromatography on silica, eluting with ethyl acetate and trituration with diethyl ether furnished the title compound (300mg) as a white powder

TLC  $R_f$  0.3 (ethyl acetate)

20

Intermediate 11 N-(2-Methylthiazolylmethyl)-3,4-dimethoxybenzenesulphonamide

25

Prepared from 2-methyl-4-aminomethylthiazole [J. Gen. Chem. USSR (English Translation), 1961, 31, 1255-9] and 3,4-dimethoxybenzenesulphonyl chloride.

Purification by column chromatography on silica, eluting with 50% ethyl acetate/hexane afforded the title compound (0.84g) as a white solid.

30

TLC  $R_f$  0.45 (ethyl acetate)

Intermediate 12 N-(4-Methoxybenzyl)-3,4-dimethoxybenzenesulphonamide

35

Recrystallization from ethyl acetate/hexane yielded the title compound (3.5g) as white crystals.

TLC  $R_f$  0.27 (50% ethyl acetate/hexane)

5 Intermediate 13 N-[4-(1,2,3-Thiadiazol-4-yl)benzyl]-3,4-dimethoxybenzenesulphonamide

Recrystallization from ethyl acetate/hexane furnished the title compound (380mg) as a white solid.

10 TLC  $R_f$  0.45 (15% ethyl acetate in dichloromethane)

15 The following compounds were prepared from 3,4-dimethoxybenzenesulphonyl chloride and the appropriate amine hydrochloride salts, using the above procedure.

15 Intermediate 14 N-(Cyanomethyl)-3,4-dimethoxybenzenesulphonamide

20 Purification by column chromatography on silica, eluting with 15% ethyl acetate in dichloromethane and recrystallization from ethyl acetate/hexane provided the title compound (68mg) as a white solid.

TLC  $R_f$  0.25 (60% ethyl acetate in hexane)

25 Intermediate 15 N-Pyrazinylmethyl-3,4-dimethoxybenzenesulphonamide

Prepared from aminomethylpyrazine hydrochloride [J. Org. Chem., 1973, 38, 2049-52].

30 Purification by column chromatography on silica, eluting with ethyl acetate gave the title compound (400mg).

TLC  $R_f$  0.2 (ethyl acetate)

35 Intermediate 16 N-(3-Bromobenzyl)-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography on silica, eluting with 50% ethyl acetate in hexane furnished the title compound (640mg) as a white crystalline solid.

5 TLC  $R_f$  0.4 (50% ethyl acetate/hexane)

Intermediate 17 N-(4-Bromobenzyl)-3,4-dimethoxybenzenesulphonamide

10 Purification by column chromatography on silica, eluting with 50% ethyl acetate in hexane and trituration with diethyl ether afforded the title compound (634mg) as a white solid.

15 TLC  $R_f$  0.35 (50% ethyl acetate in hexane)

Intermediate 18 N-Propyl-3,4-dimethoxybenzenesulphonamide

20 The title compound was obtained as a white solid (10.11g).

TLC  $R_f$  0.18 (dichloromethane)

Intermediate 19 2-(Methanesulphonyloxy)methoxybenzene

25 A solution of 2-methoxyphenol (0.65ml) in pyridine (20ml) was cooled to 0°C under a nitrogen atmosphere. After stirring for 5 minutes, methanesulphonyl chloride (0.62ml) was added dropwise, and stirring was continued for 15 minutes at 0°C followed by 1.5 hours at room temperature. The solvent was removed in vacuo and the residue partitioned between water (25ml) and ethyl acetate (25ml). The organic phase was dried (magnesium sulphate) and evaporated in vacuo.

30 The crude product was purified by column chromatography on silica, eluting with 20% ethyl acetate in hexane to furnish the title compound (1.76g) as an oil.

TLC  $R_f$  0.25 (30% ethyl acetate in hexane)

Intermediate 20 3-Methanesulphonyloxy-4-methoxybenzenesulphonyl chloride

5

A solution of 2-(methanesulphonyloxy)methoxybenzene (0.822g) in dichloromethane (15ml) was stirred and cooled to -10°C under a nitrogen atmosphere. A solution of chlorosulphonic acid (0.27ml) in dichloromethane (5ml) was 10 then added dropwise over a period of 1 hour, maintaining the temperature below 0°C. The mixture was stirred for a further 4 hours, allowing the temperature to rise to 10°C. The mixture was evaporated to dryness in vacuo to yield an 15 oil which was suspended in toluene (20ml) with stirring under a nitrogen atmosphere. Oxalyl chloride (0.36ml) was added dropwise, followed by the addition of DMF (5 drops). After stirring for 2 hours at room temperature, dichloromethane (15ml) and oxalyl chloride (0.36ml) were 20 added and the reaction stirred overnight. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica, eluting with 60% ethyl acetate in hexane to furnish the title compound (0.99g) as a white crystalline solid.

25 TLC  $R_f$  0.4 (60% ethyl acetate in hexane)

Intermediate 21 N-Benzyl-3-hydroxy-4-methoxybenzenesulphonamide

30 N-Benzyl-3-methanesulphonyloxy-4-methoxybenzenesulphonamide (0.2g) in 1M aqueous sodium hydroxide solution (5ml) was stirred at 45°C for 2 hours. The clear solution was acidified with 6M aqueous hydrochloric acid (1ml) and extracted into ethyl acetate (3 x 15ml). The combined 35 organic phases were dried (magnesium sulphate), filtered and evaporated in vacuo. The residue crystallized upon

standing to provide the title compound (0.17g) as a white crystalline solid.

TLC  $R_f$  0.47 (60% ethyl acetate in hexane)

5

The following compound was prepared from the appropriate starting material, using the above procedure.

10

Intermediate 22 N-Furfuryl-3-hydroxy-4-methoxybenzenesulphonamide

TLC  $R_f$  0.27 (60% ethyl acetate in hexane)

15

Intermediate 23 Ethyl 3-(furfurylamino)propanoate

20

Ethyl acrylate (30g) was added dropwise to a stirred solution of furfurylamine (116.5g) in toluene (400ml). The mixture was stirred overnight at room temperature, then heated at reflux for 2 hours. The solution was evaporated in vacuo and the residue was distilled to yield the title compound (45g).

b.p. 106-109°C (1.5mmHg)

25

The following compounds were prepared from the appropriate starting materials, using the above procedure.

Intermediate 24 3-(Tetrahydrofurfurylamino)propionitrile

30

Distillation afforded the title compound (64g).

b.p. 100-104°C (0.7mmHg)

Intermediate 25 3-(Furfurylamino)propionitrile

35

Intermediate 26 3-Cyclopentyloxy-4-methoxyaniline

3-Cyclopentyloxy-4-methoxybenzoic acid (10g) was heated at reflux with toluene (120ml) with azeotropic removal of water. On cooling, thionyl chloride (6.7g) and a few drops of DMF were added. The mixture was heated at reflux for 5 hours, cooled, filtered and evaporated in vacuo. A solution of this residue (26.7g) in dioxane (250ml) was added dropwise to a cooled (0°C) and stirred solution of sodium azide (8.2g) in water (250ml) and dioxane (250ml). The mixture was stirred at room temperature for 1 hour, then diluted with water (300ml) and extracted with toluene (2 x 300ml). The toluene extracts were washed with water (500ml) then dried (magnesium sulfate). This solution was added dropwise with stirring to toluene (300ml) at reflux. After addition, the solution was heated at reflux and stirred for 1 hour. Evaporation of the solvent in vacuo afforded the crude isocyanate (60g) which was then heated at reflux and stirred in absolute ethanol (400ml) for 1 hour. After evaporation of the solvent in vacuo, the resulting oil was heated at reflux and stirred with 10% aqueous sodium hydroxide solution (600ml) and ethanol (600ml) for 6 hours. On cooling, the reaction mixture was diluted with water (500ml) and extracted with dichloromethane (3 x 500ml). The organic extracts were washed with water (2 x 500ml), dried (magnesium sulphate) and evaporated in vacuo. The residue was distilled under reduced pressure to give the title compound (32g).

b.p. 128-130°C (0.3mmHg)

30

Intermediate 27 N-Benzyl-N-(4-methanesulphonyloxybenzyl)-3,4-dimethoxy-benzenesulphonamide.

Sodium hydride (60% dispersion, 26mg) was added to a stirred solution of N-benzyl-3,4-dimethoxybenzenesulphonamide (200mg) in DMF (5ml) at 0°C under a nitrogen atmosphere and the mixture stirred for 5

minutes. O-Methanesulphonyl-4-methanesulphonyloxybenzyl alcohol (200mg, prepared according to Tetrahedron, 1982, 38, 787-798) was then added and the mixture stirred for 3 hours. The DMF was removed in vacuo and the residual oil 5 partitioned between ethyl acetate (25ml) and water (25ml). The aqueous phase was further extracted with ethyl acetate (25ml); the combined organic phases were dried (magnesium sulphate), filtered and evaporated in vacuo. The crude product was recrystallized from ethyl acetate/hexane to 10 yield the title compound (253mg) as an off-white solid.

TLC  $R_f$  0.8 (15% ethyl acetate in hexane)

15 The following compounds were prepared according to the above procedure.

Intermediate 28 N-Benzyl-N-methanethiomethyl-3,4-dimethoxybenzenesulphonamide

20 Prepared using chloromethyl methyl sulphide and N-benzyl-3,4-dimethoxybenzene-sulphonamide.

Crystallization from ethyl acetate/hexane furnished the title compound (259mg) as a cream solid.

25

TLC  $R_f$  0.53 (50% ethyl acetate in hexane)

Intermediate 29 N-(3-Pyridyl)-N-methanethiomethyl-3,4-dimethoxybenzene-sulphonamide

30

Prepared using chloromethyl methyl sulphide and N-(3-pyridyl)-3,4-dimethoxybenzene-sulphonamide.

35 Crystallization from ethyl acetate/hexane gave the title compound (270mg) as a pale yellow solid.

TLC  $R_f$  0.58 (10% methanol in ethyl acetate)

Intermediate 30

O-Methanesulphonyl-3-methanesulphonyloxybenzyl alcohol.

Triethylamine (7.9ml) was added to a stirred solution of 3-hydroxybenzyl alcohol (2.0g) in dichloromethane (25ml) at 5  $0^{\circ}\text{C}$  under a nitrogen atmosphere and the solution stirred for 5 minutes. A solution of methanesulphonyl chloride (3.9ml) in dichloromethane (20ml) was added dropwise over 10 20 minutes and stirring was continued for a further 10 minutes. The reaction mixture was then washed with 5% aqueous sulfuric acid (50ml), saturated aqueous sodium hydrogen carbonate solution (50ml), water (50ml) and brine (50ml). The organic phase was dried (magnesium sulphate), filtered and evaporated in vacuo. Crystallization from 15 ethyl acetate/hexane afforded the title compound (3.7g) as an off-white solid.

TLC  $R_f$  0.55 (15% ethyl acetate/dichloromethane)

20 Intermediate 31

N-Benzyl-3-[(3-phenoxypropyl)oxy]-4-methoxybenzenesulphonamide

Cesium carbonate (55mg) was added to a stirred solution of 25 N-(benzyl)-3-hydroxy-4-methoxybenzenesulphonamide (50mg) in DMF (5ml) under a nitrogen atmosphere. 3-Phenoxypropyl bromide (0.027ml) was then added dropwise and the mixture heated for 1 hour at  $50^{\circ}\text{C}$ . The cooled mixture was poured into concentrated potassium carbonate solution (20ml) and extracted with diethyl ether (3 x 20ml). The combined 30 organic phases were dried (magnesium sulphate), filtered and evaporated under high vacuum. Trituration with diethyl ether and hexane afforded the title compound (32mg) as a white crystalline solid.

35 TLC  $R_f$  0.69 (60% ethyl acetate in hexane)

The following compound was prepared using the above procedure.

5 Intermediate 32 N-Furfuryl-3-[ (3-phenoxypropyl)oxy]-4-methoxybenzene-sulphonamide

Purification by column chromatography on silica, eluting with 55% ethyl acetate in hexane provided the title compound (116mg) as a white solid.

10 TLC  $R_f$  0.54 (60% ethyl acetate in hexane)

15 Intermediate 33 N-Furfuryl-3-cyclopentyloxy-4-methoxybenzenesulphonamide.

15 3-Cyclopentyloxy-4-methoxyaniline (15g) was diazotized in a mixture of concentrated hydrochloric acid (22ml) and water (7.5ml) using a solution of sodium nitrite (5.13g) in water (12.5ml), maintaining the temperature at 0°C. The 20 resulting solution was filtered through celite and the filtrate added to a solution of sulphur dioxide (14.5g) in glacial acetic acid (75ml) which contained copper(II) chloride (2.25g). The mixture was stirred overnight at room temperature, diluted with water and extracted with 25 dichloromethane. The extracts were washed with water, dried (magnesium sulphate) and evaporated in vacuo. The residue was dissolved in ether and filtered through celite and then through silica. The solvent was removed in vacuo to yield an oil (9.3g). A portion of this product (4.5g) 30 was dissolved in dichloromethane (50ml) and added to a solution of 3-(furfuryl amino)propionitrile (2.3g) and triethylamine (1.72g) in dichloromethane (50ml). The mixture was stirred at room temperature for 3 hours, then washed with water, dried and evaporated in vacuo to yield 35 an oil which crystallized on standing. Recrystallization from ethanol furnished the title compound (1.0g).

TLC  $R_f$  0.45 (50% ethyl acetate in hexane)

Intermediate 34

N-Furfuryl-N-(2-phthalimidoethanesulphonyl)-3,4-dimethoxy-benzenesulphonamide

5

N-Furfuryl-3,4-dimethoxybenzenesulphonamide (1.0g) was added to a cooled (0°C) suspension of sodium hydride (60% dispersion in mineral oil, 0.16g) in DMF (6ml) with stirring. After 20 minutes, a solution of 2-phthalimidoethanesulphonyl chloride (0.9g) [J. Med. Chem., 1977, 20, 1128-34] in dry DMF (6ml) was added dropwise over 10 minutes and the reaction mixture stirred at room temperature overnight. The mixture was poured into water (200ml) and extracted into ethyl acetate (2 x 50ml). The combined organic extracts were washed with aqueous sodium hydrogen carbonate solution (50ml), dilute aqueous hydrochloric acid (50ml) and brine (50ml), then dried (magnesium sulphate), filtered and evaporated in vacuo. Purification by column chromatography on silica, eluting with 20%-60% ethyl acetate in hexane furnished the title compound (240mg).

TLC  $R_f$  0.4 (5% ethyl acetate in dichloromethane)

25

Intermediate 35

N-(2-Aminoethanesulphonyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide

30

A suspension of N-furfuryl-N-(2-phthalimidoethanesulphonyl)-3,4-dimethoxybenzenesulphonamide (210mg) in 50% ethanol-THF (20ml) was heated to reflux to provide a complete solution. Hydrazine monohydrate (0.8ml) was added and after 30 minutes a white precipitate formed. The cooled reaction mixture was concentrated in vacuo. The residue was partitioned between water (60ml) and dichloromethane (50ml). The aqueous phase was further extracted with dichloromethane (50ml). The

combined organic phases were washed with water (50ml), brine (50ml) and then dried (magnesium sulphate). filtered and evaporated in vacuo to afford the title compound (140mg) as a colourless oil.

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TLC  $R_f$  0.15 (5% methanol in dichloromethane)

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Intermediate 36 N-[4-(3-Pyridyl)benzyl]-3,4-dimethoxybenzenesulphonamide

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Diethyl (3-pyridyl)borane (118mg), tetrakis(triphenylphosphine)palladium(0) (50mg) and tetrabutylammonium iodide (149mg) were placed in a flask at room temperature under nitrogen. THF (12ml) was added and stirred, followed by the addition of powdered potassium hydroxide (135mg). The stirred mixture was heated to reflux for 28h. The reaction mixture was cooled and the solvent evaporated in vacuo. The residue was partitioned between water (50ml) and ethyl acetate (50ml). The aqueous phase was reextracted with ethyl acetate (2 x 50ml). The combined organic phases were dried (magnesium sulphate), filtered and evaporated in vacuo. The residue was purified by column chromatography on silica, eluting with ethyl acetate to afford the title compound (232mg) as a pale cream crystalline solid.

TLC  $R_f$  0.2 (ethyl acetate)

30

The following compound was prepared according to the above procedure.

Intermediate 37 N-[3-(3-Pyridyl)benzyl]-3,4-dimethoxybenzenesulphonamide

35

Purification by column chromatography on silica furnished the title compound (219mg) as a white foam.

TLC  $R_f$  0.3 (ethyl acetate)

Intermediate 38 N-[2-(3-Pyridyl)benzyl]-3,4-dimethoxybenzenesulphonamide

5

Purification by column chromatography on silica furnished the title compound (112mg) as a clear oil.

TLC  $R_f$  0.33 (ethyl acetate)

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Example 1 N,N-Dibenzyl-3,4-dimethoxybenzenesulphonamide.

Dibenzylamine (10.45ml) was added to a suspension of 3,4-dimethoxybenzenesulphonyl chloride (0.50g) in dichloromethane (15ml). Triethylamine (0.44ml) was then added and the resultant solution was stirred at room temperature for 20 hours. The mixture was diluted with dichloromethane (25ml) and then washed successively with saturated aqueous sodium hydrogen carbonate solution (15ml), 2N aqueous hydrochloric acid (15ml) and brine (20ml). The solution was dried (magnesium sulphate) and concentrated in vacuo. Purification by column chromatography on silica, eluting with 25% ethyl acetate in hexane afforded the title compound (0.73g) as a colourless oil which crystallized on standing.

TLC  $R_f$  0.25 (25% ethyl acetate in hexane)

m.p. 79-80°C

30 The following compounds were prepared from 3,4-dimethoxybenzenesulphonyl chloride and the appropriate amine, using the above procedure.

35 Example 2 N-Benzyl-N-(2-phenethyl)-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica, eluting with 25% ethyl acetate in hexane provided the title compound (0.77g) as a white solid.

5 TLC  $R_f$  0.25 (25% ethyl acetate in hexane)  
m.p. 92-93°C

Example 3 N-(2-Cyanoethyl)-N-benzyl-3,4-dimethoxybenzenesulphonamide.

10 Recrystallization from ethanol furnished the title compound (12.31g).

m.p. 95-98°C

15 TLC  $R_f$  0.33 (50% ethyl acetate in hexane)

Example 4 N-(2-Cyanoethyl)-N-(tetrahydrofurfuryl)-3,4-dimethoxybenzenesulphonamide.

20 Recrystallization from ethanol provided the title compound (6.37g).

m.p. 77-80°C

TLC  $R_f$  0.18 (50% ethyl acetate in hexane)

25 Example 5 N-(2-Cyanoethyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide.

m.p. 110-112°C

30 TLC  $R_f$  0.7 (ethyl acetate)

Example 6 3-[N-Furfuryl-3,4-dimethoxybenzenesulphonamido]propanoic acid

35 2M aqueous sodium hydroxide solution (150ml) was added to a solution of ethyl 3-[N-furfuryl-3,4-dimethoxybenzenesulphonamido]propanoate (10g) in ethanol

(150ml). The mixture was stirred overnight at room temperature, then acidified with glacial acetic acid and the ethanol removed in vacuo. The suspension was allowed to cool, the product was filtered off and washed with 5 water. Recrystallization from toluene provided the title compound (6.5g) as a white solid.

m.p. 136-139°C

TLC  $R_f$  0.2 (1% acetic acid/50% ethyl acetate in hexane)

10

Example 7 N-Benzyl-N-[ (4-<sup>n</sup>propyloxy)benzyl]-3,4-dimethoxybenzenesulphonamide.

Cesium carbonate (0.11g) was added to a stirred solution of 15 N - b e n z y l - N - ( 4 - h y d r o x y ) b e n z y l - 3 , 4 - dimethoxybenzenesulphonamide (0.1g) in DMF (5ml) under a nitrogen atmosphere. 1-Bromopropane (0.03ml) was then added dropwise and the mixture heated at 75°C for 2 hours. The reaction mixture was concentrated in vacuo. The crude 20 product was dissolved in ethyl acetate, washed with 10% potassium carbonate solution then dried over magnesium sulphate and concentrated in vacuo to afford the title compound (0.10g) as a clear oil.

25 IR (Nujol)  $\nu_{\text{max}}$  1509, 1330, 1261  $\text{cm}^{-1}$ .

TLC  $R_f$  0.32 (30% ethyl acetate in hexane).

The following compounds were prepared from the appropriate starting materials, using the above procedure.

30

Example 8 N-Benzyl-N-[ (3-<sup>n</sup>propyloxy)benzyl]-3,4-dimethoxybenzenesulphonamide.

Crystallization from ethyl acetate/hexane afforded the 35 title compound (0.21g) as a white solid.

m.p. 85-86°C

TLC  $R_f$  0.32 (30% ethyl acetate in hexane).

Example 9 N-(3-Cyanopropyl)-N-(4-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide.

5

Sodium hydride (60% dispersion in oil, 29mg) was added to a solution of N-(4-

10 pyridylmethyl)-3,4-dimethoxybenzenesulphonamide (202mg) in anhydrous N,N-dimethylformamide (5ml) under an atmosphere of nitrogen at room temperature. After 30 minutes 4-bromobutyronitile (78 $\mu$ l) was added and stirring continued for 24 hours. The mixture was concentrated in vacuo, then 15 purified by column chromatography on silica eluting with 1% methanol in dichloromethane to afford the title compound as a colourless oil (125mg) that solidified on standing.

m.p. 108-110°C

TLC  $R_f$  0.25 (25% ethyl acetate in hexane)

20

The following compounds were prepared using the above general procedure from the starting sulphonamide and appropriate halide.

25 Example 10 N-(3-Cyanopropyl)-N-(2-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide.

30 Purification was achieved by column chromatography on silica eluting with 1% methanol in dichloromethane to afford the title compound (96mg) as an oil.

IR (Nujol)  $\nu_{max}$  1154, 1340, 2242  $\text{cm}^{-1}$ .

TLC  $R_f$  0.25 (1% methanol in dichloromethane).

35 Example 11 N-(3-Cyanopropyl)-N-(2,6-dichlorobenzyl)-3,4-dimethoxybenzene-sulphonamide.

Purification was achieved by column chromatography on silica eluting with 5% ethyl acetate in dichloromethane to afford the title compound (345mg) as an oil that solidified on standing.

5

m.p. 120-122°C

TLC  $R_f$  0.35 (5% ethyl acetate in dichloromethane).

10 Example 12 N-(3-Cyanopropyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide.

15 Purification was achieved by column chromatography on silica eluting with 1% methanol in dichloromethane to afford the title compound (168mg) as an oil that solidified on standing.

m.p. 86-88°C

TLC  $R_f$  0.20 (1% methanol in dichloromethane).

20 Example 13 N-(3-Cyanopropyl)-N-phenethyl -3,4-dimethoxybenzenesulphonamide.

25 Purification was achieved by column chromatography on silica eluting with 55% ethyl acetate in hexane to afford the title compound (154mg) as an oil.

IR (thin film)  $\nu_{max}$  1154, 1332, 2247  $\text{cm}^{-1}$ .

TLC  $R_f$  0.25 (50% ethyl acetate in hexane).

30 Example 14 N-Benzyl-N-(3-Cyanopropyl)-3-(3-phenoxypropoxy)-4-methoxybenzene-sulphonamide.

35 Purification was achieved by column chromatography on silica eluting with 50% ethyl acetate in hexane followed by crystallisation from ethyl acetate-hexane to afford a colourless solid (23mg).

m.p. 78-80°C

TLC  $R_f$  0.50 (60% ethyl acetate in hexane).

5 Example 15 N-(3-Cyanopropyl)-N-furfuryl-3-(3-  
phenoxypropoxy)-4-methoxybenzene-sulphonamide.

Purification was achieved by column chromatography on  
silica eluting with 50% ethyl acetate in hexane followed by  
crystallisation from ethyl acetate-hexane to afford a  
10 colourless solid (33mg).

m.p. 80-82°C

TLC  $R_f$  0.47 (60% ethyl acetate in hexane).

15 Example 16 N-(Carboethoxymethyl)-N-furfuryl-3,4-  
dimethoxybenzenesulphonamide.

Purification was achieved by column chromatography eluting  
with 50% ethyl acetate in hexane to afford the title  
20 compound as an oil that solidified on standing.

m.p. 56 -57°C

TLC  $R_f$  0.56 (60% ethyl acetate in hexane).

25 Example 17 N-(Carbomethoxymethyl)-N-furfuryl-3,4-  
dimethoxybenzenesulphonamide.

Crystallisation from ethyl acetate-hexane afforded pale  
yellow crystals (257mg).

30

m.p. 86.5 - 87.5°C

TLC  $R_f$  0.48 (60% ethyl acetate in hexane).

35 Example 18 Methyl 2-[N-(3-cyanopropyl)-3,4-  
dimethoxybenzenesulphonamido]-3-  
phenylpropionate.

Purification was achieved by column chromatography eluting with 50% ethyl acetate in hexane to afford the title compound (127mg) as an oil.

5 IR (thin film)  $\nu_{max}$  1138, 1334, 1738, 2246  $\text{cm}^{-1}$ .  
TLC  $R_f$  0.33 (50% ethyl acetate in hexane).

Example 19 N-Furfuryl-N-(2-oxopropyl)-3,4-dimethoxybenzenesulphonamide.

10 Crystallisation from ethyl acetate-hexane afforded pale yellow crystals (229mg).

m.p. 100 - 102°C

15 TLC  $R_f$  0.43 (60% ethyl acetate in hexane).

Example 20 N-Furfuryl-N-cyanomethyl-3,4-dimethoxybenzenesulphonamide.

20 Trituration of the crude product with hexane then crystallization from ethanol afforded the title compound (4.98g).

m.p. 98 -101°C

25 TLC  $R_f$  0.48 (50% ethyl acetate in hexane).

Example 21 N-(3-Cyanopropyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide.

30 Crystallization from toluene-hexane afforded the title compound.

m.p. 103 -105°C

TLC  $R_f$  0.34 (50% ethyl acetate in hexane).

Example 22 N - F u r f u r y l - N - p r o p y l - 3 , 4 - dimethoxybenzenesulphonamide.

Crystallization from ethanol afforded the title compound.

m.p. 83 -84°C

TLC  $R_f$  0.60 (50% ethyl acetate in hexane).

5

Example 23 N-Benzyl-N-(4-chlorobenzyl)-3,4-dimethoxybenzenesulfonamide.

Purification was achieved by column chromatography on 10 silica eluting with 66% diethyl ether in hexane to afford the title compound (0.61g) as a white solid.

m.p. 97-98°C

TLC  $R_f$  0.74 (50% ethyl acetate in hexane).

15

Example 24 N-Benzyl-N-(3-chlorobenzyl)-3,4-dimethoxybenzenesulphonamide.

Purification was achieved by column chromatography on 20 silica eluting with 66% diethyl ether in hexane to afford the title compound (0.46g) as a white solid.

m.p. 89-91°C

TLC  $R_f$  0.2 (66% diethyl ether in hexane).

25

Example 25 N-Benzyl-N-(2-chlorobenzyl)-3,4-dimethoxybenzenesulphonamide.

Purification was achieved by column chromatography on 30 silica eluting with 50% ethyl acetate in hexane to afford the title compound (0.57g) as a white solid.

m.p. 108-110°C

TLC  $R_f$  0.86 (50% ethyl acetate in hexane).

35

Example 26 N-Benzyl-N-(4-cyanobenzyl)-3,4-dimethoxybenzenesulphonamide.

Purification was achieved by column chromatography on silica eluting with 33% ethyl acetate in hexane to afford the title compound (2.33g) as a white solid.

5 m.p. 105-107°C  
TLC  $R_f$  0.52 (50% ethyl acetate in hexane).

Example 27 N-Benzyl-N-(3-cyanobenzyl)-3,4-dimethoxybenzenesulphonamide.

10 Purification was achieved by column chromatography on silica eluting with 75% diethyl ether in hexane to afford the title compound (2.22g) as a white solid.

15 m.p. 82-83°C  
TLC  $R_f$  0.1 (66% diethyl ether in hexane).

Example 28 N-Benzyl-N-(2-cyanobenzyl)-3,4-dimethoxybenzenesulphonamide.

20 Purification was achieved by column chromatography on silica eluting with 66% diethyl ether in hexane to afford the title compound (0.19g) as a white solid.

25 m.p. 82-83°C  
TLC  $R_f$  0.52 (66% diethyl ether in hexane).

Example 29 N-(3-Cyanopropyl)-N-(1-phenylethyl)-3,4-dimethoxybenzenesulphonamide.

30 Purification was achieved by column chromatography on silica eluting with 10% ethyl acetate in dichloromethane to afford the title compound (0.74g) as a clear oil.

35 IR (KBr disc)  $\nu_{max}$  1509, 1262, 1328  $\text{cm}^{-1}$ .  
TLC  $R_f$  0.27 (10% ethyl acetate in dichloromethane).

5           Example 30       N-Benzyl-N-(3-aminopropyl)-3,4-dimethoxybenzenesulphonamide.

10           The crude product was partitioned between ethyl acetate and 2M HCl. The aqueous phase was basified with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and concentrated in vacuo to afford the title compound (40mg) as a clear gum.

15           IR (KBr disc)  $n_{\text{max}}$  1509, 1329, 1262  $\text{cm}^{-1}$ .

20           TLC  $R_f$  0.32 (9% methanol/1% triethylamine in dichloromethane).

25           Example 31       N-Benzyl-N-(3-methanesulphonyloxy)benzyl-3,4-dimethoxybenzenesulphonamide.

20           Purification was achieved by column chromatography on silica eluting with 60% ethyl acetate in hexane to afford the title compound (2.4g) as a white solid.

25           m.p. 77-78°C

30           TLC  $R_f$  0.77 (15% ethyl acetate in dichloromethane).

25           Example 32       N-Benzyl-N-(4-methoxycarbonyl)benzyl-3,4-dimethoxybenzenesulphonamide.

30           Purification was achieved by column chromatography on silica eluting with 50% ethyl acetate in hexane to afford the title compound (1.43g) as a white solid.

25           m.p. 86-88°C

30           TLC  $R_f$  0.48 (50% ethyl acetate in hexane).

25           Example 33       N-Benzyl-N-(3-methoxycarbonyl)benzyl-3,4-dimethoxybenzenesulphonamide.

Purification was achieved by column chromatography on silica eluting with 50% ethyl acetate in hexane to afford the title compound (1.76g) as a clear, viscous oil.

5 IR (thin film)  $n_{\text{max}}$  1720, 1508, 1331  $\text{cm}^{-1}$ .  
TLC  $R_f$  0.58 (50% ethyl acetate in hexane).

Example 34 N-Benzyl-N-(2-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide.

10 Purification was achieved by column chromatography on silica eluting with 10% ethyl acetate in dichloromethane to afford the title compound (100mg) as a clear gum.

15 IR (thin film)  $n_{\text{max}}$  1508, 1329, 1262  $\text{cm}^{-1}$ .  
TLC  $R_f$  0.31 (10% ethyl acetate in dichloromethane).

Example 35 N-Benzyl-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide.

20 Purification was achieved by column chromatography on silica eluting with 75% ethyl acetate in hexane to afford the title compound (90mg) as a clear gum.

25 IR (thin film)  $n_{\text{max}}$  1508, 1331, 1139  $\text{cm}^{-1}$ .  
TLC  $R_f$  0.77 ( 75% ethyl acetate in hexane).

Example 36 N-(3-Cyanopropyl)-N-[2-(2-pyridyl)ethyl]-3,4-dimethoxybenzenesulphonamide

30 Purification by column chromatography eluting with ethyl acetate provided the title compound as a clear oil (110mg).  
TLC  $R_f$  0.22 (ethyl acetate).  
35 IR (thin film)  $n_{\text{max}}$  1589, 1509, 1139  $\text{cm}^{-1}$ .

Example 37 N,N-Di-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography eluting with 10%  
5 methanol/ 1% triethylamine in ethyl acetate provided the  
title compound as a beige solid (165mg).

TLC  $R_f$  0.08 (1% acetic acid/ 5% methanol in ethyl acetate).  
m.p. 109-110°C.

10

Example 38 N-(Carboxamidomethyl)-N-benzyl-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 40%  
15 ethyl acetate in hexane afforded the title compound as a  
white solid (74mg).

TLC  $R_f$  0.2 (40% ethyl acetate in hexane).  
m.p. 135-137°C.

20

Example 39 N-Propyl-N-[4-(3-pyridyl)benzyl]-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting  
25 with ethyl acetate furnished the above compound (181mg) as  
a white foam.

TLC  $R_f$  0.4 (ethyl acetate)  
IR  $\nu_{max}$  1587, 1508, 1464, 1403, 1330, 1261, 1237, 1152,  
30 1138, 1092, 1020  $\text{cm}^{-1}$ .

Example 40 N-Furfuryl-N-methyl-3,4-dimethoxybenzenesulphonamide.

35 Trituration with diethyl ether afforded the title compound  
(263mg) as an off-white solid.

TLC  $R_f$  0.7 (50% ethyl acetate in hexane)  
m.p. 133-134°C

5 The following compounds were prepared according to the above procedure from N-propyl-3,4-dimethoxybenzenesulphonamide and the appropriate halide.

Example 41 N-(2-Methoxycarbonylfuryl)-N-propyl-3,4-dimethoxybenzenesulphonamide.

10

Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane provided the title compound (0.59g) as a clear oil.

15

TLC  $R_f$  0.8 (15% ethyl acetate in dichloromethane)  
IR  $\nu_{max}$  1727, 1588, 1509, 1306, 1262, 1139  $\text{cm}^{-1}$ .

Example 42 N-(4-Methoxycarbonylbenzyl)-N-propyl-3,4-dimethoxybenzenesulphonamide.

20

Purification by column chromatography on silica eluting with 5% ethyl acetate in dichloromethane yielded the title compound (1.61g) as a white solid.

25

TLC  $R_f$  0.45 (50% ethyl acetate in hexane)  
m.p. 112.5 - 113.5°C

Example 43 N-Furfuryl-N-(2-hydroxyethyl)-3,4-dimethoxybenzenesulphonamide.

30

Lithium aluminium hydride (0.03g) was suspended in anhydrous tetrahydrofuran (10ml) under an atmosphere of nitrogen at room temperature. To this was added, over 15 minutes, a solution of the ethyl ester (0.20g) prepared as above, in anhydrous tetrahydrofuran (10ml). The mixture was heated at 60°C for 5 hours then stirred at room temperature for a further 24 hours. After quenching with

hydrochloric acid (4ml, 2M) the mixture was concentrated in vacuo. The residue was redissolved in ethyl acetate (20ml) then washed with dilute hydrochloric acid (20ml, 2M), water (20ml) and saturated brine (20ml). The organic phase was 5 dried over magnesium sulphate, filtered and concentrated in vacuo to yield a colourless oil.

Purification by column chromatography on silica eluting with 70% ethyl acetate in hexane followed by crystallization from ethyl acetate-hexane afforded a 10 colourless solid (34mg).

m.p. 84 -86°C

TLC  $R_f$  0.24 (60% ethyl acetate in hexane).

15 Example 44 N-Benzyl-N-ethanesulphonyl-3,4-dimethoxybenzenesulphonamide.

Sodium hydride (60% dispersion, 72mg) was added to a stirred solution of N-benzyl-3,4-dimethoxybenzenesulphonamide (500mg) in DMF (15ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 15 minutes before a solution of ethanesulphonyl chloride (230mg) in DMF (5ml) was added. The solution was allowed to warm to room temperature and stirred overnight. The 20 solvent was removed in vacuo and the residue dissolved in dichloromethane (50ml) and washed with water (2 x 20ml) and brine (20ml). The solution was dried (magnesium sulphate), 25 filtered and evaporated in vacuo.

Purification by column chromatography on silica eluting 30 with dichloromethane afforded the title compound (506mg) as a clear gum.

TLC  $R_f$  0.63 (dichloromethane)

35 IR (KBr)  $\nu_{max}$  2941, 1587, 1509, 1369, 1267, 1239, 1156, 1094, 1021  $\text{cm}^{-1}$ .

The following compounds were prepared according to the above procedure from the appropriate sulphonamide and sulphonyl chloride.

5    Example 45    N-Benzyl-N-benzenesulphonyl-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting with dichloromethane afforded the title compound (600mg) as  
10    a white solid.

m.p. 108-109°C

TLC  $R_f$  0.48 (dichloromethane)

15    Example 46    N-Benzyl-N-methanesulphonyl-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane and subsequent  
20    recrystallization from ethyl acetate/hexane yielded the title compound (0.92g) as a white solid.

m.p. 113-114.5°C

TLC  $R_f$  0.36 (50% ethyl acetate/hexane)

25    Example 47    N-Methanesulphonyl-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting  
30    with ethyl acetate and recrystallization from ethyl acetate/hexane furnished the title compound (553mg) as a white solid.

m.p. 121-122°C

35    TLC  $R_f$  0.42 (ethyl acetate)

Example 48 N-Benzyl-N-(2-phthalimidoethanesulphonyl)-3,4-dimethoxybenzene-sulphonamide.

Purification by column chromatography on silica eluting  
5 with 3% ethyl acetate in dichloromethane yielded the title  
compound (240mg) as a white solid.

m.p. 160-161°C

TLC  $R_f$  0.75 (5% ethyl acetate/dichloromethane)

10

Example 49 N-Methanesulphonyl-N-[2-(2-pyridyl)ethyl]-3,4-dimethoxybenzene-sulphonamide

Purification by column chromatography eluting with 35%  
15 ethyl acetate-hexane provided the title compound as a clear  
oil (19mg).

TLC  $R_f$  0.35 (35% ethyl acetate in hexane).

IR (thin film)  $\nu_{max}$  1590, 1510, 1364, 1159  $\text{cm}^{-1}$ .

20

Example 50 N-Methanesulphonyl-N-[1,2,3-thiadiazol-4-yl]benzyl]-3,4-dimethoxy-benzenesulphonamide

Purification by column chromatography eluting with 55%  
25 ethyl acetate-hexane and subsequent trituration with  
diethyl ether provided the title compound as a white solid  
(94mg).

TLC  $R_f$  0.35 (55% ethyl acetate in hexane).

30 m.p. 172-173°C.

Example 51 N-Methanesulphonyl-N-(4-methoxybenzyl)-3,4-dimethoxybenzene-sulphonamide

35 Purification by column chromatography eluting with 33%  
ethyl acetate-hexane provided the title compound as a white  
solid (2.6g).

TLC  $R_f$  0.43 (50% ethyl acetate in hexane).  
m.p. 149-150°C.

5 Example 52 N-Methanesulphonyl-N-(2-pyridylmethyl)-3,4-dimethoxybenzene-sulphonamide

Purification by column chromatography eluting with 50% ethyl acetate-hexane afforded the title compound as a colourless solid (100mg).

10 TLC  $R_f$  0.74 (ethyl acetate).  
m.p. 123-124°C.

15 Example 53 N-Methanesulphonyl-N-pyrazinylmethyl-3,4-dimethoxybenzene-sulphonamide

Purification by column chromatography eluting with ethyl acetate provided the title compound as a white solid (100mg).

20 TLC  $R_f$  0.45 (ethyl acetate).  
m.p. 141-142°C.

25 Example 54 N-Methanesulphonyl-N-[4-(3-pyridyl)benzyl]-3,4-dimethoxybenzene-sulphonamide.

Purification by column chromatography eluting with ethyl acetate and subsequent trituration with diethyl ether/hexane provided the title compound as a white solid (61mg).

TLC  $R_f$  0.33 (ethyl acetate).  
m.p. 132-134°C.

35 Example 55 N-Methanesulphonyl-N-[3-(3-pyridyl)benzyl]-3,4-dimethoxybenzene-sulphonamide

Purification by column chromatography eluting with ethyl acetate and subsequent evaporation in vacuo from diethyl ether/hexane provided the title compound as a white foam (56mg).

5

TLC  $R_f$  0.3 (ethyl acetate).

IR (thin film)  $\nu_{max}$  1509, 1366, 1265, 1159  $\text{cm}^{-1}$ .

10 Example 56 N-Methanesulphonyl-N-[2-(3-pyridyl)benzyl]-

3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with ethyl acetate and subsequent evaporation in vacuo from diethyl ether provided the title compound as an off-white foam

15 (26mg).

TLC  $R_f$  0.35 (ethyl acetate)

IR  $\nu_{max}$  1587, 1509, 1366, 1266, 1159, 1142  $\text{cm}^{-1}$ .

20 Example 57 N-Furfuryl-N-methanesulphonyl-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 50% ethyl acetate-hexane provided the title compound as a clear oil (400mg) which solidified on standing.

TLC  $R_f$  0.5 (50% ethyl acetate in hexane).

m.p. 110-112°C.

30 Example 58 N-(2-Phthalimidoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

Purification by crystallisation from ethyl acetate/hexane provided the title compound as a cream solid (236mg).

35

TLC  $R_f$  0.56 (10% methanol in ethyl acetate)

m.p. 177-178°C.

Example 59 N-Methanesulphonyl-N-(2-methylthiazol-4-ylmethyl)-3,4-dimethoxy-benzenesulphonamide

Purification by column chromatography eluting with 5 50%ethyl acetate-hexane provided the title compound as a white solid (250mg).

TLC  $R_f$  0.75 (ethyl acetate).

IR (thin film)  $\nu_{max}$  1509, 1367, 1266, 1160  $\text{cm}^{-1}$ .

10

The following compounds were prepared by the above procedure from N-benzyl-3,4-dimethoxybenzenesulphonamide, the appropriate acid chloride and a reaction time of 4 days.

15

Example 60 N-Benzoyl-N-benzyl-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting 20 with dichloromethane gave the title compound (0.57g) as a white solid.

m.p. 104°C

TLC  $R_f$  0.38 (dichloromethane)

25

Example 61 N-Benzyl-N-propionyl-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting 30 with dichloromethane yielded the title compound (0.44g) as a clear gum.

TLC  $R_f$  0.3 (dichloromethane)

IR  $\nu_{max}$  2941, 1702, 1588, 1511, 1457, 1408, 1357, 1266, 35 1240, 1161, 1141, 1092, 1020  $\text{cm}^{-1}$ .

Example 62      N-[2-Amino(N-benzenesulphonyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

5      Triethylamine (500 $\mu$ l) was added to a suspension of N-(2-Aminoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide (1.22g) in dichloromethane (20ml) at 0°C under an inert atmosphere. Benzenesulphonylchloride (340 $\mu$ l) was then added and the 10 resultant solution was stirred at room temperature overnight. The mixture was diluted with dichloromethane (20ml) and washed with 50% saturated sodium hydrogen carbonate solution (40ml). The solution was dried over magnesium sulphate and concentrated in vacuo. The residue 15 was purified by column chromatography eluting with 5% methanol in ethyl acetate to provide the title compound as a pale yellow solid (630mg).

20      TLC R<sub>f</sub> 0.56 (10% methanol in ethyl acetate).  
m.p. 68-70°C.

The following compounds were prepared from the appropriate starting materials using the above procedure.

25      Example 63      N-[2-Amino(N-benzoyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

30      Purification by column chromatography eluting with 5% methanol in ethyl acetate provided the title compound as a white solid (20mg).

TLC R<sub>f</sub> 0.61 (10% methanol in ethyl acetate).  
m.p. 134-135.5°C.

35      Example 64      N-[2-(N,N-Dibenzenesulphonyl)aminoethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 1%-5% methanol in dichloromethane afforded the title compound as a yellow oil (120mg).

5 TLC  $R_f$  0.46 (4% methanol in dichloromethane).  
IR (thin film)  $\nu_{max}$  1509, 1377, 1267, 1168  $\text{cm}^{-1}$ .

Example 65 N-[2-Amino(N-benzenesulphonyl)ethanesulphonyl]-N-furfuryl-3,4-dimethoxybenzenesulphonamide

Purification by column chromatography eluting with 20%-50% ethyl acetate in hexane provided the title compound as an off-white semi-solid (120mg).

15 TLC  $R_f$  0.35 (50% ethyl acetate in hexane).  
IR (thin film)  $\nu_{max}$  1509, 1374, 1266, 1160  $\text{cm}^{-1}$ .

Example 66 N-Benzyl-N-(3-hydroxybenzyl)-3,4-dimethoxybenzenesulphonamide.

Aqueous sodium hydroxide solution (1M, 25ml) was added to a solution of N-benzyl-N-(3-methanesulphonyloxybenzyl)-3,4-dimethoxybenzenesulphonamide (2.0g) in 1,4-dioxane (25ml) 25 and the mixture heated at 85°C for 3 hours. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (75ml) and 2M aqueous hydrochloric acid (75ml). The aqueous layer was further extracted with ethyl acetate (75ml) and the combined organic phases were dried 30 (magnesium sulphate), filtered and evaporated in vacuo. Crystallization from diethyl ether/hexane afforded an off-white solid (1.5g).

m.p. 107-108°C  
35 TLC  $R_f$  0.47 (15% ethyl acetate in dichloromethane)

The following compound was prepared by the above procedure using the appropriate starting material.

5           Example 67       N-Benzyl-N-(4-hydroxybenzyl)-3,4-dimethoxybenzenesulphonamide.

Purification by column chromatography on silica eluting with 15% ethyl acetate in dichloromethane afforded the title compound as a clear oil.

10           TLC  $R_f$  0.6 (15% ethyl acetate in dichloromethane)  
IR (thin film)  $\nu_{max}$  3447, 2936, 1614, 1590, 1509, 1326, 1263, 1238, 1138, 1094, 1020  $\text{cm}^{-1}$ .

15           Example 68       N-Benzyl-N-(4-carboxamidobenzyl)-3,4-dimethoxybenzenesulphonamide.

Oxalyl chloride (0.09ml) was added to a stirred suspension of N-benzyl-N-(4-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide (0.43g) in dichloromethane (5ml), under a nitrogen atmosphere. DMF (2 drops) was then added and stirring was continued at room temperature for a further 90 minutes. Ammonium hydroxide solution (8ml) was added to the reaction; the resulting precipitate was filtered off, washed with water and dried in vacuo. The crude solid was recrystallized from ethyl acetate/hexane to afford the title compound (0.13g) as a white solid.

20           m.p. 172°C  
30           TLC  $R_f$  0.42 (ethyl acetate).

The following compounds were prepared from the appropriate starting materials, using the above procedure.

35           Example 69       N-Benzyl-N-(3-carboxamidobenzyl)-3,4-dimethoxybenzenesulphonamide.

The title compound (0.20g) was obtained as a white solid.

m.p. 146-148°C

TLC R<sub>f</sub> 0.38 (ethyl acetate).

5

Example 70 N-(4-Carboxamidobenzyl)-N-propyl-3,4-dimethoxybenzenesulphonamide.

The title compound (0.21g) was obtained as a white solid.

10

m.p. 173 - 175°C

TLC R<sub>f</sub> 0.45 (ethyl acetate)

15

Example 71 N-Benzyl-N-[4-(N-methyl)carboxamidobenzyl]-3,4-dimethoxybenzenesulphonamide.

20

Oxalyl chloride (0.09ml) was added to a stirred suspension of N-benzyl-N-(4-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide (0.43g) in dichloromethane (5ml), under a nitrogen atmosphere. DMF (2 drops) was then added and stirring was continued at room temperature for a further 90 minutes. The reaction mixture was then added to aqueous methylamine solution (40%, 10ml). After stirring for a further 60 minutes, the layers were separated. The organic phase was washed with dilute hydrochloric acid (25ml), water (20ml), brine (20ml), dried over magnesium sulphate and concentrated in vacuo. The crude solid was recrystallized from ethyl acetate/hexane to afford the title compound (0.39g) as a white solid.

25

m.p. 140-142°C

TLC R<sub>f</sub> 0.41 (ethyl acetate).

30

The following compounds were prepared using the appropriate starting materials, using the above procedure.

Example 72 N-Benzyl-N-[3-(N-methyl)carboxamidobenzyl]-

## 3,4-dimethoxybenzene-sulphonamide.

The title compound (0.28g) was obtained as a white solid.

5 m.p. 102-104°C

TLC  $R_f$  0.44 (ethyl acetate).

Example 73 N-[4-(N-Methyl)carboxamidobenzyl]-N-propyl-3,4-dimethoxybenzene-sulphonamide.

10

The title compound (0.26g) was obtained as a white solid.

m.p. 151.5 - 153°C

TLC  $R_f$  0.4 (ethyl acetate)

15

Example 74 N-[4-(N,N-Dimethyl)carboxamidobenzyl]-N-propyl-3,4-dimethoxybenzene-sulphonamide.

The title compound (0.35g) was obtained as a clear oil.

20

TLC  $R_f$  0.35 (ethyl acetate)

IR  $\nu_{max}$  2964, 2934, 1632, 1588, 1509, 1462, 1404, 1330, 1262, 1237, 1153, 1092, 1019  $\text{cm}^{-1}$ .

25

Example 75 N-Benzyl-N-(4-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide.

30

N-Benzyl-N-(4-methoxycarbonyl)benzyl-3,4-dimethoxybenzenesulphonamide (1.1g) was dissolved in tetrahydrofuran (20ml), treated with aqueous lithium hydroxide (0.2g in water (20ml)) and then stirred for 24 hours at room temperature. Concentration in vacuo gave a residue which was diluted with water and acidified with concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water and concentrated in vacuo to afford the title compound (1.07g) as a white solid.

m.p. 193-195°C

TLC  $R_f$  0.28 (50% ethyl acetate in hexane).

5 The following compounds were prepared from the appropriate starting materials, using the above procedure.

Example 76 N-Benzyl-N-(3-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide.

10 The title compound (0.97g) was obtained as a white solid.

m.p. 55-57°C

TLC  $R_f$  0.27 (50% ethyl acetate in hexane).

15 Example 77 N-(2-Carboxyfuryl)-N-propyl-3,4-dimethoxybenzenesulphonamide.

The title compound (0.44g) was obtained as a white solid.

20 TLC  $R_f$  0.1 (50% ethyl acetate in hexane)

m.p. 152.5-153.5°C

Example 78 N-4-Carboxybenzyl-N-propyl-3,4-dimethoxybenzenesulphonamide.

25

The title compound (1.41g) was obtained as a white solid.

TLC  $R_f$  0.14 (50% ethyl acetate in hexane)

m.p. 151 - 152.5°C

30

Example 79 N-Benzyl-N-(methanesulphonylmethyl)-3,4-dimethoxybenzenesulphonamide

35 A solution of oxone™ (390mg) in water (2ml) was added to a stirred solution of N-Benzyl-N-(methanethiomethyl)-3,4-dimethoxybenzenesulphonamide (150mg) in methanol (5ml) at 0-5°C. The resultant slurry was stirred at 0-5°C for 1 hour

and then at room temperature overnight. The reaction mixture was partitioned between diethyl ether (2x30ml) and water (30ml) and the combined organic phases were dried over magnesium sulphate and concentrated in vacuo.

5 Purification by recrystallisation from ethyl acetate/hexane afforded the title compound as a pale yellow solid (99mg).

TLC  $R_f$  0.31 (50% ethyl acetate in hexane).

m.p. 117-118°C.

10

The following compound was prepared from the appropriate starting materials, using the above procedure.

15 Example 80 N-(Methanesulphonylmethyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

Purification by recrystallisation from ethyl acetate/hexane provided the title compound as a cream solid (275mg).

20 TLC  $R_f$  0.45 (10% methanol in ethyl acetate).  
m.p. 124.5-126°C.

25 Example 81 N-[2-Amino(N-pyridin-3-oyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

N-(2-Aminoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide (240mg), nicotinic acid (71mg), 1-hydroxybenzotriazole (172mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (240mg) in dichloromethane (10ml) and tetrahydrofuran (5ml) were stirred at room temperature overnight under an inert atmosphere. The resulting solution was diluted with dichloromethane (20ml) and extracted with 50% saturated sodium hydrogen carbonate solution (40ml). The organic phase was dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography eluting with 1% triethylamine/10% methanol in ethyl acetate

and subsequently crystallised using dichloromethane/hexane to provide the title compound as a white solid (142mg).

5       TLC  $R_f$  0.16 (10% methanol in ethyl acetate)  
m.p. 149-150.5°C.

Example 82       N-[2-Amino(N-Benzyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

10      Benzaldehyde (62 $\mu$ l) was added to a stirred solution of N-(2-aminoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide (250mg) in dichloromethane (10ml) under an inert atmosphere. Sodium triacetoxyborohydride (190mg) was then added and the 15 reaction stirred at room temperature overnight. The resulting solution was diluted with dichloromethane (40ml) and extracted with 50% saturated sodium hydrogen carbonate solution (50ml). The organic phase was dried over magnesium sulphate and concentrated in vacuo. The residue 20 was purified by column chromatography on silica eluting with 1% triethylamine/ 7.5% methanol in ethyl acetate providing the title compound as a clear oil (81mg).

25       TLC  $R_f$  0.36 (10% methanol in ethyl acetate).  
IR (thin film)  $\nu_{max}$  1509, 1371, 1265, 1155  $cm^{-1}$ .

The following compound was prepared using the appropriate starting materials using the above procedure.

30      Example 83       N-[2-Amino(N,N-dibenzyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

35      Purification by column chromatography eluting with 1% triethylamine/ 7.5% methanol in ethyl acetate provided the title compound as a pale yellow oil (59mg).

TLC  $R_f$  0.67 (10% methanol in ethyl acetate).

IR (thin film)  $n_{\max}$  1509, 1372, 1266, 1157  $\text{cm}^{-1}$ .

Example 84 N-(2-Aminoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxy-benzenesulphonamide

5

Hydrazine monohydrate (1.21ml) was added to a solution of N-(2-Pthalimidoethane-sulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide (290mg) in ethanol (10ml) and tetrahydrofuran (10ml) at reflux. After stirring at reflux for 30 minutes the reaction was cooled to room temperature and water (2.5ml) was added. The resulting solution was concentrated in vacuo, with the residue being partitioned between saturated sodium hydrogen carbonate solution (40ml) and dichloromethane (2x40ml). The organic phase was dried over magnesium sulphate and concentrated in vacuo to yield the title compound as a yellow oil (220mg).

TLC  $R_f$  0.09 (1% triethylamine/10% methanol in ethyl acetate).

20 IR (thin film)  $n_{\max}$  1509, 1369, 1266, 1156  $\text{cm}^{-1}$ .

The following compound was prepared using the appropriate starting materials using the above procedure.

25 Example 85 N-Benzyl-N-(2-aminoethanesulphonyl)-3,4-dimethoxybenzene-sulphonamide

Purification was achieved by partitioning the crude residue between 1M hydrochloric acid (40ml) and dichloromethane (2x40ml). The aqueous phase was then basified to pH 14 using sodium hydroxide pellets and subsequently extracted with dichloromethane (2x100ml). The organic phase was dried over magnesium sulphate and concentrated in vacuo to provide the title compound as a clear oil (61mg).

35

TLC  $R_f$  0.42 (10% methanol in ethyl acetate)

IR (thin film)  $n_{\max}$  1509, 1369, 1266, 1155  $\text{cm}^{-1}$ .

Assay methods

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (i) are standard assay procedures as disclosed by Schilling et al  
5 Anal. Biochem. 216 154 (1994), Thompson and Strada Adv. Cycl. Nucl. Res. 8 119 (1979) and Gristwood and Owen Br. J. Pharmacol. 87 91P (1986).

Compounds of formula (i) have exhibited activity at levels  
10 consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

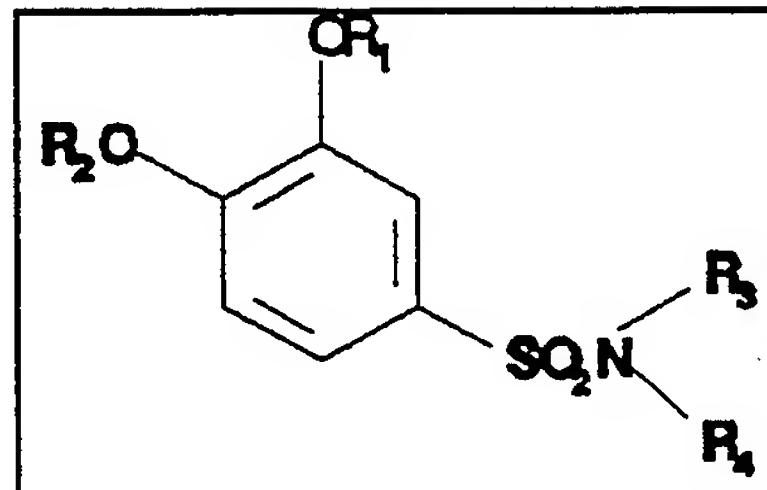
CLAIMS

## 1. Compounds of the general formula (i)

5

10

(i)



15

in which  $R_1$  represents  $C_{1-6}$  alkyl (optionally substituted with one or more substituents chosen from amongst halogen,  $C_{1-6}$  alkoxy, aryloxy, arylalkyloxy,  $C_{1-6}$  alkylamino, arylalkylamino or arylamino) or cycloalkyl (optionally substituted with one or more substituents chosen from amongst halogen,  $C_{1-6}$  alkoxy, aryloxy, arylalkyloxy,  $C_{1-6}$  alkylamino, arylalkylamino or arylamino);

$R_2$  represents  $C_{1-3}$  alkyl optionally substituted with halogen;

$R_3$  represents arylalkyl, heteroarylalkyl, heterocycloalkyl,  $COR_7$ ,  $S(O)_mR_7$ ,  $C_{1-6}$  alkyl optionally substituted with one or more substituents chosen from amongst hydroxy,  $C_{1-6}$  alkoxy,  $-CO_2H$ ,  $CO_2R_8$ ,  $SO_2NR_9R_{10}$ ,  $CONR_9R_{10}$ ,  $-CN$ , carbonyl oxygen,  $NR_5R_6$ ,  $COR_7$ ,  $S(O)_nR_7$ ,

$R_4$  represents arylalkyl, heteroarylalkyl or heterocycloalkyl;

35

when  $R_3$  and/or  $R_4$  represents arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion may be optionally

substituted with one or more substituents chosen from amongst  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{R}_8$ ,  $\text{SO}_2\text{NR}_9\text{R}_{10}$ ,  $\text{CONR}_9\text{R}_{10}$ , hydroxy,  $\text{C}_{1-6}$  alkoxy,  $\text{NR}_5\text{R}_6$ ,  $\text{COR}_7$ ,  $\text{S(O)}_n\text{R}_7$ , -CN or carbonyl oxygen and/or the aryl/heteroaryl/heterocyclo portion may be optionally substituted with one or more substituents  $\text{C0-6 alkyl-R}_{11}$ ;

$\text{R}_5$  and  $\text{R}_6$ , which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo,  $\text{C}_{1-6}$  alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl,  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl heteroarylcarbonyl, heterocyclocarbonyl or  $\text{C}_{1-6}$  alkylsulphonyl, provided that when  $\text{R}_5$  is  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or  $\text{C}_{1-6}$  alkylsulphonyl,  $\text{R}_6$  is not  $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, heteroarylcarbonyl, heterocyclocarbonyl, arylcarbonyl or  $\text{C}_{1-6}$  alkylsulphonyl;

$\text{R}_7$  represents aryl, heteroaryl, heterocyclo or  $\text{C}_{1-6}$  alkyl, any of which may be optionally substituted with one or more substituents chosen from amongst halogen, aryl, heteroaryl, heterocyclo,  $\text{C}_{1-6}$  alkoxy, hydroxy,  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{R}_8$ ,  $\text{SO}_2\text{NR}_9\text{R}_{10}$ ,  $\text{CONR}_9\text{R}_{10}$ ,  $\text{NR}_5\text{R}_6$ , or carbonyl oxygen;

$\text{R}_8$  represents  $\text{C}_{1-6}$  alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$\text{R}_9$  and  $\text{R}_{10}$ , which may be the same or different, each represent H, aryl, heteroaryl, heterocyclo,  $\text{C}_{1-6}$  alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl;

$\text{R}_{11}$  represents H, aryl, heteroaryl, heterocyclo, hydroxy,  $\text{C}_{1-6}$  alkoxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy,  $-\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{R}_8$ ,  $\text{SO}_2\text{NR}_9\text{R}_{10}$ ,  $\text{CONR}_9\text{R}_{10}$ ,

halogen, -CN, -NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>n</sub>R<sub>7</sub>, -CN or carbonyl oxygen;

m represents 1-2; and

5 n represents 0-2;

and pharmaceutically acceptable salts thereof, and, where applicable, all stereoisomers including enantiomers and diastereoisomers and mixtures including racemic mixtures  
10 thereof.

2. A compound of claim 1, wherein

when R<sub>3</sub> is alkyl, any substituents are selected from  
15 OH, alkoxy, COOH, (and C<sub>1-6</sub> alkyl esters and C<sub>1-6</sub> alkyl amides thereof), CN, carbonyl oxygen, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub> and S(O)<sub>0-2</sub>R<sub>7</sub>;

for R<sub>4</sub>, and when R<sub>3</sub> is arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion is optionally substituted by COOH (and C<sub>1-6</sub> alkyl esters and C<sub>1-6</sub> alkyl amides thereof), OH, alkoxy, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>0-2</sub>R<sub>7</sub>, CN or carbonyl oxygen, and the aryl/heteroaryl/heterocyclo portion is optionally substituted by one or more of aryl, heteroaryl, heterocyclo, OH, alkoxy, COOH (and C<sub>1-6</sub> alkyl esters and C<sub>1-6</sub> alkyl amides thereof), halogen, CN, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>0-2</sub>R<sub>7</sub> and alkyl optionally substituted by one or more of aryl, heteroaryl, heterocyclo, COOH (and C<sub>1-6</sub> alkyl esters and C<sub>1-6</sub> alkyl amides thereof), OH, alkoxy, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub>, S(O)<sub>0-2</sub>R<sub>7</sub>, CN and carbonyl oxygen;

R<sub>5</sub> and R<sub>6</sub> are independently selected from H, alkyl, alkylcarbonyl, alkoxy carbonyl, arylsulphonyl, arylcarbonyl and alkylsulphonyl;

35

R<sub>7</sub> is alkyl optionally substituted by one or more of halogen, aryl, heteroaryl, alkoxy, OH, COOH, (and C<sub>1-6</sub> alkyl

esters and C<sub>1-6</sub> alkyl amides thereof), NR<sub>5</sub>R<sub>6</sub>, S(O)<sub>0-2</sub>R<sub>8</sub> and carbonyl oxygen; and

R<sub>8</sub> is alkyl, aryl or heteroaryl.

5

3. A compound of claim 2, wherein R<sub>1</sub> is alkyl or cycloalkyl, either being optionally substituted by halogen, alkoxy, aryloxy or arylalkoxy; and

10

R<sub>3</sub> is arylalkyl, heteroarylalkyl, heterocycloalkyl or alkyl optionally substituted by OH, alkoxy, COOH (or C<sub>1-6</sub> alkyl esters or C<sub>1-6</sub> alkyl amides thereof), COOalk, CN or carbonyl oxygen;

15

for R<sub>4</sub> and when R<sub>3</sub> is arylalkyl, heteroarylalkyl or heterocycloalkyl, the alkyl portion is optionally substituted by OH, alkoxy, for COOH (or C<sub>1-6</sub> alkyl esters or C<sub>1-6</sub> alkyl amides thereof), NR<sub>5</sub>R<sub>6</sub>, CN or carbonyl oxygen, and the aryl/heteroaryl/heterocyclo portion is optionally substituted by OH, alkoxy, COOH (or C<sub>1-6</sub> alkyl esters or C<sub>1-6</sub> alkyl amides thereof), halogen, CN or NR<sub>5</sub>R<sub>6</sub>.

20

4. A compound of any preceding claim wherein R<sub>1</sub> is alkyl optionally substituted by aryloxy, or cycloalkyl.

25

5. A compound of any preceding claim, wherein R<sub>2</sub> is methyl optionally substituted by halogen.

30

6. A compound of any preceding claim, wherein R<sub>3</sub> is arylalkyl, heteroarylalkyl, COR<sub>7</sub>, S(O)<sub>1-2</sub>R<sub>7</sub> or optionally-substituted alkyl and R<sub>4</sub> is arylalkyl or heteroarylalkyl;

the aryl or heteroaryl portion is optionally substituted by C<sub>0-6</sub> alkyl-R<sub>11</sub>;

35

R<sub>5</sub> and R<sub>6</sub> are independently selected from H, alkyl, alkylcarbonyl, alkylsulphonyl, aryl, heteroaryl,

70

arylsulphonyl, heteroarylsulphonyl, arylcarbonyl, heteroarylcarbonyl, arylalkyl and heteroarylalkyl;

5        R<sub>7</sub> is aryl, heteroaryl, or alkyl optoinally substituted by CN, COOH, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, carbonyl oxygen or NR<sub>5</sub>R<sub>6</sub>;

R<sub>8</sub> is alkyl;

10        R<sub>9</sub> and R<sub>10</sub> are independently selected from H, alkyl, arylalkyl and heteroarylalkyl; and

15        R<sub>11</sub> is aryl, heteroaryl, OH, alkoxy, CN, COOH, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>, carbonyl oxygen, NR<sub>5</sub>R<sub>6</sub>, COR<sub>7</sub> or SO<sub>2</sub>R<sub>7</sub>.

7.        A compound of claim 1, selected from

N,N-Dibenzyl-3,4-dimethoxybenzenesulphonamide,

20        N-Benzyl-N-(2-phenethyl)-3,4-dimethoxybenzenesulphonamide,

N-(2-Cyanoethyl)-N-benzyl-3,4-dimethoxybenzenesulphonamide,

25        N-(2-Cyanoethyl)-N-(tetrahydrofurfuryl)-3,4-dimethoxybenzenesulphonamide,

3-[N-Furfuryl-3,4 dimethoxybenzenesulphonamido]propanoic acid,

30        N-(3-Cyanopropyl)-N-(4-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-(3-Cyanopropyl)-N-(2-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

35        N-(3-Cyanopropyl)-N-(2,6-dichlorobenzyl)-3,4-dimethoxybenzenesulphonamide,

N-(3-Cyanopropyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

5 N-(3-Cyanopropyl)-N-phenethyl-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-(3-Cyanopropyl)-3-(3-phenoxypropoxy)-4-methoxybenzenesulphonamide,

10 N-(3-Cyanopropyl)-N-furfuryl-3-(3-phenoxypropoxy)-4-methoxybenzenesulphonamide,

N-(Carboethoxymethyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide,

15 N-(Carbomethoxymethyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide,

20 Methyl 2-[N-(3-cyanopropyl)-3,4-dimethoxybenzenesulphonamido]-3-phenylpropionate,

N-Furfuryl-N-(2-oxopropyl)-3,4-dimethoxybenzenesulphonamide,

25 N-Furfuryl-N-cyanomethyl-3,4-dimethoxybenzenesulphonamide,

N-(3-Cyanopropyl)-N-furfuryl-3,4-dimethoxybenzenesulphonamide,

30 N-Furfuryl-N-propyl-3,4-dimethoxybenzenesulphonamide,

N-Furfuryl-N-(2-hydroxyethyl)-3,4-dimethoxybenzenesulphonamide.

35 8. A compound of claim 1, selected from

N-(2-cyanoethyl)-N-furfuryl-3,4-  
dimethoxybenzenesulphonamide,  
5  
N-Benzyl-N-[ (4-<sup>n</sup>propyloxy)benzyl]-3,4-  
dimethoxybenzenesulphonamide,  
N-Benzyl-N-[ (3-<sup>n</sup>propyloxy)benzyl]-3,4-  
dimethoxybenzenesulphonamide,  
10 N-Benzyl-N-(4-chlorobenzyl)-3,4-  
dimethoxybenzenesulfonamide,  
N-Benzyl-N-(3-chlorobenzyl)-3,4-  
dimethoxybenzenesulphonamide,  
15 N-Benzyl-N-(2-chlorobenzyl)-3,4-  
dimethoxybenzenesulphonamide,  
N-Benzyl-N-(4-cyanobenzyl)-3,4-  
20 dimethoxybenzenesulphonamide,  
N-Benzyl-N-(3-cyanobenzyl)-3,4-  
dimethoxybenzenesulphonamide,  
25 N-Benzyl-N-(2-cyanobenzyl)-3,4-  
dimethoxybenzenesulphonamide,  
N-(3-Cyanopropyl)-N-(1-phenylethyl)-3,4-  
dimethoxybenzenesulphonamide,  
30 N-Benzyl-N-(3-aminopropyl)-3,4-  
dimethoxybenzenesulphonamide,  
N-Benzyl-N-(3-methanesulphonyloxy)benzyl-3,4-  
35 dimethoxybenzenesulphonamide,

N-Benzyl-N-(4-methoxycarbonyl)benzyl-3,4-dimethoxybenzenesulphonamide,

5 N-Benzyl-N-(3-methoxycarbonyl)benzyl-3,4-dimethoxybenzenesulphonamid,

N-Benzyl-N-(2-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

10 N-Benzyl-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-ethanesulphonyl-3,4-dimethoxybenzenesulphonamide,

15 N-Benzyl-N-benzenesulphonyl-3,4-dimethoxybenzenesulphonamide,

20 N-Benzyl-N-methanesulphonyl-3,4-dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

25 N-Benzyl-N-(2-phthalimidoethanesulphonyl)-3,4-dimethoxybenzenesulphonamide,

N-Benzoyl-N-benzyl-3,4-dimethoxybenzenesulphonamide,

30 N-Benzyl-N-propionyl-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-(3-hydroxybenzyl)-3,4-dimethoxybenzenesulphonamide,

35 N-Benzyl-N-(4-hydroxybenzyl)-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-(4-carboxamidobenzyl)-3,4-dimethoxybenzenesulphonamide,

5 N-Benzyl-N-(3-carboxamidobenzyl)-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-[4-(N-methyl)carboxamidobenzyl]-3,4-dimethoxybenzenesulphonamide,

10 N-Benzyl-N-[3-(N-methyl)carboxamidobenzyl]-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-(4-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide,

15 N-Benzyl-N-(3-carboxybenzyl)-3,4-dimethoxybenzenesulphonamide.

9. A compound of claim 1, selected from

20 N-(3-Cyanopropyl)-N-[2-(2-pyridyl)ethyl]-3,4-dimethoxybenzenesulphonamide,

N,N-Di-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

25 N-(Carboxamidomethyl)-N-benzyl-3,4-dimethoxybenzenesulphonamide,

30 N-Propyl-N-[4-(3-pyridyl)benzyl]-3,4-dimethoxybenzenesulphonamide,

N-Furfuryl-N-methyl-3,4-dimethoxybenzenesulphonamide,

35 N-(2-Methoxycarbonylfuryl)-N-propyl-3,4-dimethoxybenzenesulphonamide,

N-(4-Methoxycarbonylbenzyl)-N-propyl-3,4-  
dimethoxybenzenesulphonamide,

5 N-Methanesulphonyl-N-[2-(2-pyridyl)ethyl]-3,4-  
dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-[1,2,3-thiadiazol-4-yl]benzyl]-3,4-  
dimethoxybenzenesulphonamide,

10 N-Methanesulphonyl-N-(4-methoxybenzyl)-3,4-  
dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-(2-pyridylmethyl)-3,4-  
dimethoxybenzenesulphonamide,

15 N-Methanesulphonyl-N-pyrazinylmethyl-3,4-  
dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-[4-(3-pyridyl)benzyl]-3,4-  
20 dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-[3-(3-pyridyl)benzyl]-3,4-  
dimethoxybenzenesulphonamide,

25 N-Methanesulphonyl-N-[2-(3-pyridyl)benzyl]-3,4-  
dimethoxybenzenesulphonamide,

N-Furyl-N-methanesulphonyl-3,4-  
dimethoxybenzenesulphonamide,

30 N-(2-Phthalimidoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-  
dimethoxybenzenesulphonamide,

N-Methanesulphonyl-N-(2-methylthiazol-4-ylmethyl)-3,4-  
35 dimethoxybenzenesulphonamide,

N-[2-Amino(N-benzenesulphonyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

5 N-[2-Amino(N-benzoyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-[2-(N,N-Dibenzenesulphonyl)aminoethanesulphonyl]-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

10 N-[2-Amino(N-benzenesulphonyl)ethanesulphonyl]-N-furfuryl-3,4-dimethoxybenzenesulphonamide,

N-(4-Carboxamidobenzyl)-N-propyl-3,4-dimethoxybenzenesulphonamide,

15 N-[4-(N-Methyl)carboxamidobenzyl]-N-propyl-3,4-dimethoxybenzenesulphonamide,

20 N-[4-(N,N-Dimethyl)carboxamidobenzyl]-N-propyl-3,4-dimethoxybenzenesulphonamide,

N-(2-Carboxyfurfuryl)-N-propyl-3,4-dimethoxybenzenesulphonamide,

25 N-4-Carboxybenzyl-N-propyl-3,4-dimethoxybenzenesulphonamide,

N-Benzyl-N-(methanesulphonylmethyl)-3,4-dimethoxybenzenesulphonamide,

30 N-(Methanesulphonylmethyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

35 N-[2-Amino(N-pyridin-3-oyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

N-[2-Amino(N-Benzyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

5 N-[2-Amino-(N,N-dibenzyl)ethanesulphonyl]-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide

N-(2-Aminoethanesulphonyl)-N-(3-pyridylmethyl)-3,4-dimethoxybenzenesulphonamide,

10 N-Benzyl-N-(2-aminoethanesulphonyl)-3,4-dimethoxybenzenesulphonamide

10. A compound of claim 1, in the form of an enantiomer or diastereoisomer, or any mixture of either.

15 11. A pharmaceutical composition containing a compound according to any of claims 1 to 10 as active ingredient, in combination with suitable excipients.

20 12. A method for treating a disease state capable of being modulated by inhibiting production of phosphodiesterase IV, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

25 13. The method of claim 12, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

30 14. The method of claim 13, wherein the pathological condition is selected from asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the 35 eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis and other arthritic conditions, ulcerative colitis, Crohn's disease,

adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic dermatitis, atopic eczema, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, 5 cardiac arrest, stroke and intermittent claudication.

15. The method of claim 14, wherein the pathological condition is asthma.

10 16. A method for treating a disease state capable of being modulated by inhibiting TNF, comprising administering to a patient suffering from said disease an effective amount of a compound according to any of claims 1 to 10.

15 17. The method of claim 16, wherein the disease state is an inflammatory disease or autoimmune disease.

18. The method of claim 17, wherein the disease state is selected from joint inflammation, arthritis, rheumatoid 20 arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, asthma, bone 25 resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection, fever and myalgias due to infection, such as influenza, malaria, myalgias, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, 30 systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukaemia.

35 19. The method of claim 18, wherein the disease state is joint inflammation.

20. The method of claim 12 or claim 16, wherein the disease state is tardive dyskinesia.

21. The method of claim 16, wherein the disease state is  
5 a yeast or fungal infection.

22. A method for gastroprotection, comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1 to 10.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/01204

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07C311/29	C07D307/52	C07D213/42	A61K31/18	C07D307/14
	C07C311/48	C07D209/48	C07D285/06	C07D241/12	C07D401/12
	C07D277/28	C07C311/51	C07C317/28	C07D213/82	C07C311/32

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 02465 (RHONE-POULENC RORER) 3 February 1994 cited in the application see page 6 - page 7 ---	1,11-13
A	EP,A,0 497 564 (RHONE-POULENC RORER) 5 August 1992 see page 2; claims ---	1,11-13
A	US,A,4 948 809 (E.-C. WITTE, ET AL.) 14 August 1990 see column 17, line 1 - line 9 ---	1,11
X	EP,A,0 326 170 (MITSUBISHI KASEI) 2 August 1989 see page 2 -----	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*&\* document member of the same patent family

2

Date of the actual completion of the international search

14 August 1996

Date of mailing of the international search report

21.08.96

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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/GB96/01204

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 12-22 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/GB 96/01204

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9402465	03-02-94	AU-B- CA-A- EP-A- FI-A- HU-A- JP-T- NO-A- PL-A- ZA-A-	4717693 2140441 0652868 950375 72656 8503925 950319 307265 9305448	14-02-94 03-02-94 17-05-95 27-01-95 28-05-96 30-04-96 27-03-95 15-05-95 19-05-94
EP-A-497564	05-08-92	AT-T- AU-B- AU-B- AU-B- CA-A- CZ-A- DE-D- EP-A- EP-A- ES-T- WO-A- HU-A- JP-T- NZ-A- SK-A- ZA-A-	132134 664694 1188192 4565196 2101423 9301528 69207017 0569414 0669311 2081563 9212961 64942 6504782 241427 80993 9200547	15-01-96 30-11-95 27-08-92 02-05-96 29-07-92 13-04-94 08-02-96 18-11-93 30-08-95 01-03-96 06-08-92 28-03-94 02-06-94 26-08-94 08-12-93 03-05-93
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